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CAPACITY OF REINNERVATED MUSCLES TO FUNCTION EFFICIENTLY AFTER PROLONGED DENERVATION

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THE CHANGES which develop in a muscle which has been deprived of its nerve supply are now well known, though several details relating to the processes involved remain obscure. It is generally recognized, however, that prolonged denervation ultimately leads to a condition which is incompatible with the restoration of useful function, even though the muscle has been satisfactorily reinnervated. Despite its considerable practical importance, there is still no reliable information as to the point at which the changes become irreversible. The object of this paper is to provide data relating to the reinnervation of human muscles after long periods of denervation and their capacity to function effciently offer such reinnervation. An attempt has also been made to ascertain the extent to which the residual defect after delayed nerve repair is attributable to changes in the nerve itself and how much it is due to progressive changes in the denervated muscle.

According to Gutmann and Young,[1] who have given a lucid account of the reinnervation of muscle in the rabbit after various periods of atrophy, the effectiveness of the reinnervation is prejudiced as the period of denervation increases; they discuss the factors they consider to be responsible for this. With reference to human muscle, they stated:

> . . . If the muscles atrophy at approximately the same rate as those here studied it seems likely that their recovery after such long periods of atrophy (a year) can be at best only partial. . . . It is not yet possible to say exactly what period of denervation will make these effects serious in man. They all operate increasingly from the beginning of denervation and perhaps begin to be severe after 6-9 months.

In a further experimental study of rabbit material, Gutmann[2] concluded:

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This study was aided by a grant from the National Health and Medical Research Council of Australia.

1. Gutmann, E., and Young, J. Z.: The Re-Innervation of Muscle After Various Periods of Atrophy, J. Anat. **78**:15, 1944.

2. Gutmann, E.: Effect of Delay of Innervation on Recovery of Muscle After Nerve Lesions, J. Neurophysiol. **11**:279, 1948.

. . . Up to a period of 8 months denervation, the poor degree of functional recovery following reinnervation is due to deficient maturation of the nerve fibres and to deficiency of the newly formed contact between nerve and muscle fibres. . . . After longer periods, recovery of muscle fibres becomes more deficient, the degree of muscle atrophy being then apparently a decisive factor limiting functional recovery.

It is important to remember, however, that these assessments of the effectiveness of reinnervation after varying periods of atrophy rest essentially on morphological studies of the reinnervated tissue, and not on any measurement of the extent and quality of the functional recovery. Thus, Gutmann and Young were unable to decide whether the "slower recovery of the muscle fibers which become innervated prejudices the ultimate recovery of diameter and contraction." Moreover, though Gutmann included reflex spreading of the toes as a measure of the extent of the recovery in his animals, such reflex effects are of questionable value in the precise evaluation of voluntary motor recovery. For these reasons the conclusions based on these experimental studies are not final since the consequences of the reduced innervation on function must remain inferential. Furthermore, animal experimentation deprives the investigator of the opportunity of measuring the functional response to voluntary effort, which is the critical test of the effectiveness of reinnervation and the principal objective, on the motor side, of the repair of injured nerves. It therefore becomes all the more desirable to have precise information relating to the quality of the voluntary motor recovery which can follow the reinnervation of human muscles after long periods of denervation.

Though there is much clinical information to the effect that reinnervated human muscles are capable of contracting voluntarily after prolonged denervation, references to this recovery are not sufficiently precise to permit an accurate end result assessment of the extent and quality of muscle function. For this reason, the available clinical data are of no real value in deciding the maximum period of denervation which is compatible with good functional recovery.

Though the restoration of function is specifically under review in this paper, the morphology of the denervated muscle is also of importance. Strangely enough, the histological examination of denervated human muscle has not been the subject of intensive investigation, owing, no doubt, to the difficulty of obtaining suitable material. Bowden and Gutmann,[3] from the biopsy of denervated human muscle, found that "few, if any, muscle fibers have undergone complete disintegration after 3 years' denervation," but that "from 3 years onwards the possibility of any useful recovery is in question." This estimate of the survival

3. Bowden, R. E. M., and Gutmann, E.: Denervation and Re-Innervation of Human Voluntary Muscle, Brain **67**:273, 1944.

time of denervated muscle greatly exceeds that reached on the basis of experimental inquiry, though recent observations on the opossum (Sunderland and Ray [4]) have shown that striated muscles survive denervation for 485 days in a grossly atrophied, but histologically recognizable, form.

MATERIAL

The information reported is from the personal records of a series of 59 patients with peripheral nerve sutures who were treated in the 115th Australian Military Hospital over the period from 1941 to 1946. A follow-up study of patients on their discharge was possible through the cooperation of the Repatriation Department. In this way, an unbroken record of the sequence of events following nerve repair was obtained, which in all the cases selected for this inquiry extended over four years. Furthermore, these patients were under my care throughout most, if not all, of the period of their incapacity. This considerably reduced the difficulties of maintaining records introduced by the transference of patients from clinic to clinic, which brought them under the care of a succession of medical officers, none of whom was able to make prolonged observations. As further advantage, it was possible to conduct review examinations of patients with one class of injury at the same time and in this way to compare and grade accurately the end results.

Of this series of 59 patients, 10 were considered suitable for a study of the capacity of muscles to function efficiently after reinnervation following prolonged periods of denervation. The criteria for selection were as follows: (*a*) The period of denervation to exceed six months. This was assessed on the basis of the interval elapsing between injury and repair plus the time taken for regenerating axons to reach the muscle.

(*b*) Sufficient recovery of muscular function to justify the inclusion of the case.

(*c*) The injury to be confined to one nerve. Multiple injuries often complicate the evaluation of the function and the residual wasting of individual muscles, owing to variations in the course, rate and extent of recovery in the different nerves.

(*d*) Absence of direct injury to the muscles and periarticular structures. Such injuries obscure the residual defect attributable to denervation and prevent an accurate assessment of the motor recovery attributable to the reinnervation.

(*e*) Patients to be retained under observation for a sufficiently long period to insure that a final end result was obtained.

The restriction of cases in compliance with these conditions considerably reduced the amount of material which was available for investigation. Though the series is small, it is felt that there is sufficient detail to make the observations important.

Information relating to the injury, the repair, the treatment and the course of recovery in the cases reported in this paper has been given in considerable detail elsewhere.[5]

EVALUATION OF EXTENT AND QUALITY OF MOTOR RECOVERY

Duration of Period of Denervation.—It is to be noted that the period of denervation exceeds the interval elapsing between the injury and the

4. Sunderland, S., and Ray, L. J.: Denervation Changes in Mammalian Striated Muscle, J. Neurol., Neurosurg. & Psychiat. **13**:159, 1950.

5. Sunderland, S.: Observations on the Course of Recovery and Late End Results in a Series of Cases of Peripheral Nerve Suture, Australian & New Zealand J. Surg. **18**:264, 1949.

repair, owing to the additional time, subsequent to repair, taken by the regenerating axons to reach the muscle. The period, however, is never as great as the interval between the injury and the onset of recovery, since regenerating axons reach the muscle and induce their effects there long before the appearance of voluntary contractions. Considering the influence of the level of the injury, the time taken for regenerating axons to enter the distal stump and the rate at which they advance peripherally (Sunderland [6]), it can be said that in most of the cases selected for study it would not have been possible for regenerating axons to have reached the muscles within two months of repair, and even this must be regarded as a conservative estimate, and one which errs on the side of being too low. On this basis, two months should be added to the interval between injury and repair in order to provide for the shortest possible period of denervation.

Onset and Course of Recovery.—Palpable or visible contraction of the muscle, or movement which was undoubtedly attributable to its action alone, was the criterion adopted for detecting returning function. Due regard was paid to the possibility of transmitted contraction and trick movements.[7] In order to detect the earliest signs of recovery, patients were examined at weekly intervals until all muscles were contracting; from then onward the examinations were conducted at one month, then three month and, finally, six month intervals. When weekly examinations were not possible and the first appearance of recovery could not therefore be given accurately to a specific week, the last date when the muscle was known to be still paralyzed and the date when recovery was first detected are given.

Quality of Recovery.—The end result for each movement was expressed in terms of its range and power as compared with these values for the corresponding movement on the opposite side. The range was measured with a protractor, and the power, with spring balances. To record the power, the part was voluntarily carried through the full range of movement possible and was maintained in that position against tension applied through a cuff encircling the part. The recorded power was that required to initiate movement against voluntary resistance. The process was then repeated on the opposite side. In the tables, the range and power are expressed as percentages of the normal.

In estimating the range and power, every care was taken to eliminate the compensatory action of uninvolved muscles, though this was sometimes difficult. For example, when one was testing flexion of the little

6. Sunderland, S.: Rate of Regeneration in Human Peripheral Nerves: Analysis of Interval Between Injury and Onset of Recovery, Arch. Neurol. & Psychiat. **58**:251 (Sept.) 1947; correction, **59**:416 (March) 1948.

7. Sunderland, S.: Voluntary Movements and the Deceptive Action of Muscle in Peripheral Nerve Lesions, Australian & New Zealand J. Surg. **13**:160, 1944.

finger at the metacarpophalangeal joint with the phalanges fully extended (ulnar intrinsic musculature), it was difficult to exclude the action of the flexor digitorum sublimis (and the flexor digitorum profundus when this muscle was supplied entirely from the median nerve or when the ulnar lesion was situated below the origin of the branches to the muscle). Immediately flexion occurred at the interphalangeal joints during the test, it was accepted that the long flexor was participating; the range and power were then recorded.

When it was not possible to dissociate the action of muscles normally combining with the involved muscle in the production of movements (e. g., the flexor carpi radialis and the flexor carpi ulnaris in producing flexion of the wrist), no attempt was made to assess function in terms of range and power. The state of contraction was accordingly described in such cases as strong, weak or feeble, depending on (1) the amount of residual wasting; (2) the prominence, as ascertained by inspection and palpation, of the muscle and its tendon on full contraction; (3) the power and efficiency of the movement which it was assisting to produce, and (4) the extent to which the compensatory action of other muscles was required to assist the movement, e. g., the flexor pollicis longus compensating for the adductor pollicis.

In the case of the ulnar nerve, assessment of the degree of recovery in the ulnar intrinsic muscles was supplemented from observations on (1) the amount of hypothenar elevation occurring on opposition of the thumb and little finger,[8] which provided a measure of the recovery, particularly in the opponens pollicis, and (2) the absence of a residual griffe deformity of the ring and little fingers, or, when present, the extent to which it was developed.

Wasting.—The residual wasting was expressed in terms of the difference between the circumferences of (1) the forearms, 7.5 cm. below the medial epicondyle of the humerus; (2) the hands, at the level of the fully radially abducted thumb, and (3) the legs, 20 cm. below the upper border of the patella, with the limb relaxed in the fully extended position. Measurements were not taken when the parts were affected by extensive soft tissue injury and/or edema. The assessment of the motor recovery on the basis of measurements of the circumference of the limbs was complicated by the development of a "use hypertrophy" in the uninvolved limb, which frequently obscured the true amount of residual wasting.

Electromyography.—Electromyographic equipment was not available. However, it is considered that, though desirable, this was not essential for the purposes of the present inquiry, which was concerned

8. Sunderland, S.: The Significance of Hypothenar Elevation in Movements of Opposition of the Thumb, Australian & New Zealand J. Surg. **13**:155, 1944.

with the response to voluntary effort as expressed in movement and the power with which it could be executed. Thus, if a patient could, after recovery, perform a full range of movement without impaired power and could employ the reinnervated muscles in movements demanding the coordinated activity of groups of muscles, it was considered that there was little need for electromyographic data. Such data, however, would have been most useful in investigating the basis of the residual motor disability after nerve repair.

TABLE 1.—*Motor Recovery of Radial Nerve*

			ONSET OF MOTOR RECOVERY					
			Return of Voluntary Contraction, in Weeks, Dating from Time of Repair*					
Case No.	Initials	Interval, in Days, Between Injury and Repair	B. R.	E. C. R. L.	E. D. C.	E. C. U.	A. P. L.	E. P. L.
40	K. H. McN.	313	Intact	20	34	35	40	40
332	O. J. P. L..	235	†	13 to 40	13 to 40	13 to 40	13 to 40	13 to 40
166	J. C.	207	..	..	9	9	18	19 to 25

EXTENT AND QUALITY OF MOTOR RECOVERY			
Patient	K. H. McN.	O. J. P. L.	J. C.
Interval between injury and repair	313 days	235 days	207 days
Interval between repair and last examination	330 wk.	228 wk.	240 wk.
Extension of hand	Full/Full	75/75	Full/Full
Radial deviation of hand	Not measured	Full/40	Not measured
Ulnar deviation of hand	Not measured	50/5	Not measured
Power of grip	70	30	70
Synergic extension at wrist	Good	Occurs up to 100 lb.	Good
Extension of fingers			
Simultaneous	Full/75	Full/40	Full/75
Independent			
Index	75/4	90/25	Full/4
Middle	Full/35	90/20	Full/12
Little	75/5	90/10	Full/7
Thenar abduction	80/35	80/50	Full/5
Thenar extension	Full/50	Full/40	Full/20
Wasting§			
(*a*) When maximal	35 mm.	Exceeding 25 mm.	18 mm.
(*b*) At the last examination	7 mm.	18 mm.	No wasting

* B. R. indicates brachioradialis; E. C. R. L., extensor carpi radialis longus; E. D. C., extensor digitorum communis; E. C. U., extensor carpi ulnaris; A. P. L., abductor pollicis longus; E. P.L., extensor pollicis longus.

† There was no note in the records as to the condition of this muscle following the injury; it was contracting weakly when I first examined the patient, 40 weeks after the repair.

‡ Range and power of movements are expressed as percentages of those on the normal side. The value for the range precedes that for the power.

§ Wasting is expressed as the difference in the circumference of the forearms, expressed in millimeters.

OBSERVATIONS AND COMMENT

Details relating to the interval elapsing between (1) the injury and repair and (2) the repair and the onset of recovery in individual muscles are given in table 1 (for the radial nerve) and table 2 (for the ulnar nerve), together with the end result assessments of the extent and quality of the function in the recovered muscles. Information relating

to these particular features for sciatic and median nerve suture, respectively, is contained in the following two case histories (clinical details have been provided elsewhere [5]):

CASE 122.—On Dec. 28, 1942, P. H. sustained a perforating bullet wound of the left buttock, which resulted in a comminuted fracture of the acetabulum and the head and neck of the femur and complete severance of the sciatic nerve. The wound

TABLE 2.—*Motor Recovery of Ulnar Nerve*

ONSET OF MOTOR RECOVERY

Case No.	Initials	Interval in Days, Between Injury and Repair	Return of Voluntary Contraction, in Weeks, Dating from Time of Repair*†			
			F. C. U.	F. D. P.	H.	D. I.
207	A. J. S.	131	14	20	67	81
38	J. L.	191	..	..	17	47
183	C. P. C.	272	28	†	63	†
269	C. T. B.	277	11	18	46	62
266	R. J. N.	724	7	7	77 to 197	No recovery

EXTENT AND QUALITY OF MOTOR RECOVERY

Patient	A. J. S.	J. L.	C. P. C.	C. T. B.	R. J. N.
Interval between injury and repair	131 days	191 days	272 days	277 days	724 days
Interval between repair and last examination	230 wk.	278 wk.	221 wk.	227 wk.	214 wk.
Flexor carpi ulnaris	Strong	..	Strong	Strong	Strong
Flexor digitorum profundus	Weak	..	..	Strong	Weak
Hypothenar elevation in opposition	Trace	Good	None	Some	None
Main en griffe deformity	Fully corrected	Fully corrected	Slight	Fully corrected	Fully corrected
Flexion of little finger	Full/12	50/25	Full/50	Full/33	30/0
Abduction of little finger	50/20	Full/15	Full/30	75/25	Full/0
Adduction of little finger	0/0	Flicker	Feeble	Flicker/0	No recovery
Abduction of index finger	40/15	60/15	By median nerve	33/15	No recovery
Wasting§					
(*a*) Forearm					
When maximal	20 mm.	—	Not measured	Not measured	Not measured
At the last examination	10 mm.	—	4 mm.	+0.5 mm.	5 mm.
(*b*) Hand					
When maximal	31 mm.	30 + mm.	30 mm.	35 mm.	25 mm.
At the last examination	6 mm.	15 mm.	10 mm.	0	14 mm.

* F. C. U. indicates flexor carpi ulnaris; F. D. P., flexor digitorum profundus; H., hypothenar group of muscles; D. I., first dorsal interosseous muscle.

† Partly or entirely supplied by the median nerve.

‡ Range and power of movements are expressed as percentages of those on the normal side. The value for the range precedes that for the power.

§ Wasting is expressed as the difference in the circumference of (*a*) the forearms and (*b*) the hand in the plane of the fully radially abducted thumb.

became infected, and this, together with treatment of the bone injury, delayed nerve repair, which was not performed until 249 days after the injury. At this time, the biceps muscle was not contracting, and the knee could be flexed only feebly, with gravity eliminated, by weak contractions of the medial hamstring muscles, which had commenced to contract eight weeks after the injury.

Progress Report.—The duration of the interval between repair and the onset of recovery in the various muscles was as follows: biceps, 18 weeks; calf muscles,

45 to 57 weeks; tibialis anterior, 98 to 116 weeks, and flexor hallucis longus, 231 to 256 weeks. There was no recovery in any of the remaining muscles.

When the patient was last examined, 283 weeks after the repair, there was no residual impairment of knee flexion; the biceps muscle stood out prominently on forced flexion and did not appear to be reduced in bulk, as compared with the corresponding muscle on the normal side. The foot could be fully plantar flexed, and the power of this movement was 75 per cent of that recorded on the opposite side. There was no significant recovery in the remaining muscles.

CASE 333.—On Feb. 23, 1945, J. R. L. sustained extensive mortar bomb wounds of the right elbow. There was mild sepsis of the wounds, with complete loss of function in the field of the median nerve, and the brachial artery was twice ligated, once in the wound and later in the midupper arm. In this patient there were an associated injury of the ulnar nerve and some direct soft tissue injury of the muscles arising from the medial epicondyle of the humerus. The ulnar nerve recovered spontaneously. The median nerve was repaired in the cubital fossa 245 days after the injury.

Progress Report.—The duration of the interval between repair and the onset of recovery in the various muscles was as follows: pronator teres, flexor carpi radialis and palmaris longus, 27 to 34 weeks; flexor digitorum sublimis, 47 to 67 weeks; flexor pollicis longus and flexor digitorum profundus (index), 81 to 92 weeks, and the thenar muscles, 92 to 117 weeks.

When the patient was last examined, 235 weeks after repair, motor function was recorded as follows:

Pronation: Range, 75 per cent; power, 25 per cent.

Wrist flexion: Full range; power, 75 per cent. The flexor carpi radialis was standing out prominently on flexion, and residual paresis in the flexor carpi ulnaris contributed to the residual paresis of wrist flexion.

Thenar movements: The terminal phalanx could be fully flexed, but the power was reduced to 10 per cent of that on the normal side. Movements attributable to the intrinsic muscles were strongly and well executed; this was principally due to the compensatory activity of the fibers of the intrinsic muscles supplied by the ulnar nerve, but recovery in the field of the median nerve was a contributing factor.

Movements of the index finger: For the flexor digitorum profundus, the range was 75 per cent and the power 30 per cent; for the flexor digitorum sublimis, the range was 90 per cent and the power 15 per cent.

The extent of the original wasting attributable to the lesion in the median nerve was obscured by the associated injury to the ulnar nerve. When the patient was last examined, there was 17 mm. of wasting of the forearm.

An analysis of the data provided by the observations reveals that very good or complete restoration of function may follow reinnervation of some muscles after periods of denervation of up to at least 12 months, provided that the axons can be directed in sufficient numbers to their original, or functionally similar, end organs and that the quiescent muscle has been maintained in the best possible condition by appropriate therapy.

It remains, however, to account for the residual paresis in those muscles which failed to recover completely, since the possibility remains

that the duration of denervation may have been a responsible factor in limiting the recovery in these muscles. This introduces for consideration the basis of the residual functional defect in reinnervated muscle.

The residual paresis of a reinnervated muscle may be due to a reduction in the number of its functioning units, to a reduction in the functional efficiency of individual reinnervated fibers or to a combination of the two factors. For convenience, these two factors will be considered separately.

Reduction in Number of Functioning Units.—At least four factors combine to reduce the number of muscle fibers which survive and are satisfactorily reinnervated.

1. Loss, by degeneration, of muscle fibers before regenerating axons reach them. It has been demonstrated experimentally, however, that muscles denervated for periods up to 485 days show only an occasional degenerating and degenerated fiber (Sunderland and Ray [4]), while the histological examination of biopsy material from denervated human muscles has revealed that "few, if any, muscle fibers have undergone complete disintegration after 3 years' denervation" (Bowden and Gutmann [3]).

2. Failure of axons to reach the muscle in sufficient numbers and from appropriate neurons, for the following reasons:

(*a*) A reduction in the number of surviving neurons as the result of retrograde degeneration, together with the failure of some regenerating axons to reach endoneurial tubes of the distal stump. This means that many muscle fibers are never reinnervated.

(*b*) Fiber mixing at the suture line, whereby axons enter foreign endoneurial tubes and are directed to functionally unrelated end organs, so that the reconstituted pathway is of no functional value.

3. Failure of functionally appropriate axons to reestablish continuity with their old end organs after entering the muscle and their inability to induce the formation of new ones, owing to changes, such as fibrosis, which have developed as a result of the denervation.

4. Failure of axons which have reestablished satisfactory end organ contacts to mature into pathways which will excite activity in the reinnervated muscle fiber. This may be due to one or a combination of persistent defects in the neuron, irreversible changes in the endoneurial tube or irreversible changes in the muscle. That it is not due to muscle atrophy of at least 140 days' duration is suggested by the observation [9]

9. Aitken, J. T.; Sharman, M., and Young, J. Z.: Maturation of Regenerating Nerve Fibres with Various Peripheral Connexions, J. Anat. **81**:1, 1947.

that "the maturation of the nerve fibers is as rapid when they become united with muscles allowed to atrophy for 100 or 140 days as when they grow direct into freshly denervated muscle." Furthermore, there is some evidence that atrophy of endoneurial tubes of 12 months' duration does not retard the descent of regenerating axons, nor does it prevent those changes in the restored axonal pathways which convert them into functionally efficient pathways.[10]

Reduction in Functional Efficiency of Surviving Reinnervated Muscle Fibers.—This may be due to several factors: (*a*) Failure of some axons to reestablish continuity with an original end organ and, instead, the formation of a new one. Such new end organs are probably less efficient than the old.

(*b*) Fiber mixing at the site of repair, which distorts the normal pattern of innervation sufficiently to render it less efficient.

(*c*) Failure of axons which have reestablished continuity with appropriate end organs to mature fully owing, for example, to incomplete recovery of the neuron from retrograde changes. This would reduce the efficiency of the entire peripheral motor unit. Reference has been made to the possible adverse influence of irreversible shrinkage of the endoneurial tube on the maturation of regenerated axons. It is also conceivable that the persistence of retrograde and transneuronal effects may adversely affect complicated patterns of motor activity. Thus, Campbell [11] described the loss of the proprioceptor component of the segmental spinal reflex during the period of chromatolysis which follows section of the ventral roots of peripheral nerves in the cat.

(*d*) Residual defects in the sensory reinnervation of the muscle which contribute to the motor disability.

(*e*) The possibility of overloading neurons as a result of the branching of their regenerating axons, with ultimate reinnervation of a larger field than that originally served by the neurons. These additional pathways make additional demands on the neurons, so that they are unable to direct the normal functioning of the original mass of tissue supplied. The significance of this factor, however, remains obscure.

(*f*) Failure of the satisfactorily reinnervated muscle fiber to recover fully owing to changes developing within the muscle fiber itself as a result of the prolonged denervation.

(*g*) Intramuscular changes, such as fibrosis, which may increase with the period of denervation and which would impair the coordinated activity of groups of muscle fibers. In our experience, significant

10. Sunderland.[5] Sunderland, S., and Bradley, K. C.: Endoneurial Tube Shrinkage in the Distal Segment of a Severed Nerve, J. Comp. Neurol., to be published.

11. Campbell, B.: The Effects of Retrograde Degeneration upon Reflex Activity of Ventral Horn Neurons, Anat. Rec. **88**:25, 1944.

fibrosis does not develop in denervated muscles which have been well cared for but makes its appearance when the parts have been neglected and subjected to prolonged immobilization.

The loss of some fibers and the reduced efficiency of others may be offset by the "use hypertrophy" of those fibers which have fully recovered, while reeducation may compensate to some extent for the defect arising as a result of the erroneous cross shunting of regenerating fibers at the suture line.

On the basis of the results of their experimental investigations, Gutmann and Young [1] attributed the residual impairment of muscle function following reinnervation after long periods of denervation to at least three factors:

1. "The proportion of old plates which is reinnervated falls rapidly as atrophy proceeds," and "the increasing difficulty and slowness with which new plates are formed."
2. "Prolonged atrophy increases the probability of wrong functional connexions by adding to the chances of the nerve union scar further possibilities of confusion in the muscle itself." In this way, the pattern of innervation becomes more and more abnormal as the period of denervation increases.
3. As a result of the morphologic alterations of the muscle fiber, the number of muscle fibers which never become reinnervated increases.

It is apparent from their account that these authors believed the essential factor responsible for the residual functional disability after prolonged denervation to be resident within the muscle.

According to Gutmann,[2] "the degree of recovery of function was clearly deficient" after periods of denervation (induced by repeated crushing of the nerve) of six and eight months. This "poor degree of functional recovery" was attributed to "deficient maturation of the nerve fibres and to deficiency of the newly formed contact between nerve and muscle fibres." This explanation of the residual functional defect is open to question. In the first place, the reflex spreading of the toes employed by him to assess functional recovery is hardly an acceptable test on which to base precise estimates of such recovery. Second, Gutmann, reporting on the same material, stated that "the recovery of muscle fibre size and weight was only slightly impaired even after a delay of reinnervation of 8 months," which is unlikely if maturation and the "newly formed" neuromuscular contacts were defective. It is felt that more attention should have been devoted to other factors influencing the extent and quality of the recovery. In his investigation, Gutmann stated the belief that he had excluded, as two potential sources of error in his calculations, retrograde neuronal changes

and the loss of regenerating axons as the result of erroneous fiber mixing at the site of the lesion. First, he was in error when he inferred that because nerve cells can recover from retrograde effects, all the affected neurons do so. The possibility that the reaction proceeds to degeneration in some neurons was not considered by him. Furthermore, since the retrograde effects are proportional to the severity of the injury and its proximity to the neurons, it follows that recurrent trauma in the form of repeated crushings high in the thigh, where the lesions were made in his experiments, would be likely to result in severer retrograde changes than would a single crush. For this reason, retrograde effects could have been responsible, in his experiments, for a significant reduction in the number of surviving axons after repeated crushings.

Gutmann's second inference implied that repeated crushing did not disturb the normal intrafunicular architecture at the site of injury, so that the original fiber pattern was fully retained as regeneration proceeded. In the absence of histological examination of the crushed area, this is a highly contentious point, and it is my experience that the normal intrafunicular anatomy can rarely be consistently and completely preserved with repeated crushing. Even preservation of funicular continuity does not necessarily exclude rupture of the endoneurial tubes and intrafunicular hemorrhages or fibrosis, all of which complicate the subsequent course of regeneration. When the endoneurial tubes are ruptured, the regenerating axons are no longer confined to their original tubes, and, since the funiculi at the level of the injury contain fibers from several sources, some fiber mixing is certain to occur, despite the fact that the funiculi are in continuity. The extent to which this fiber mixing disarranges the original pattern is determined, *inter alia*, by such factors as the number of fibers whose sheaths are breached in this way, the composition of the tissue at the site of the injury, the amount of budding of individual regenerating axons and the number of fibers destined for each branch. In any event, the arrangement of fibers high in the thigh and the intrafunicular pathology are such that the loss of some regenerating axons along foreign pathways is inevitable. This loss is naturally accentuated when the funiculi are severed, since the axons may then regenerate outside the nerve and into the epineurial tissue of the distal stump, and this represents a further reduction in the number of fibers available for the reinnervation of the denervated muscles.

Finally, Gutmann based his estimate of the residual defect after delayed reinnervation on the results of a comparison of the function (reflex spreading of the toes), fiber size and muscle weight observed three months after the onset of recovery following immediate crushing, on the one hand, and repeated crushing, on the other. This is hardly

a fair test of the capacity of muscles denervated for long periods to recover on reinnervation. After an immediate crush the onset of recovery varied from 52 to 55 days, indicating that regenerated axons had reached the muscles prior to this, so that the duration of denervation must have been well under two months. The expected loss of muscle weight and fiber atrophy after such a period of denervation would not have exceeded (according to Gutmann's data) 40 to 50 and 29 to 50 per cent, respectively. On the other hand, after eight months' denervation the values for loss of weight and fiber atrophy would be 74 and 70 per cent. It might be expected that, after reinnervation, muscle fibers would recover more slowly from such an advanced condition of atrophy than those which had sustained a much milder degree of atrophy. Though Gutmann observed that "the initial weight is almost completely regained in 12 weeks" after immediate crushing and that "the initial average diameter of muscle fibre size is regained about the same time," there is no evidence that the condition observed after the same interval in material subjected to prolonged denervation before reinnervation represents the end point of recovery. Experience indicates that an interval of three months subsequent to the onset of recovery is too short to permit accurate end result assessments. In other words, the procedure adopted by Gutmann tested the nature of the recovery after a three month period, rather than the capacity of the reinnervated muscle to recover completely. After studying his data, one is left with the impression that retrograde neuronal effects and incomplete recovery must have contributed to the residual defect recorded by him after prolonged denervation.

In any event, the important point is that Gutmann did not believe the factor responsible for the defective recovery after periods of denervation of up to eight months' duration to be resident in the muscle fiber. However, after periods of denervation exceeding eight months he stated that "recovery of muscle fibres becomes more deficient, the degree of muscle atrophy being then apparently a decisive factor in limiting functional recovery." The evidence advanced in support of this thesis is not convincing, however, and other factors which influence the extent and quality of the recovery after nerve suture were not excluded.

The experimental investigations have given an exceedingly clear picture of the complexities of reinnervation processes and the manner in which the restored pattern becomes progressively more distorted as the period of denervation increases, until ultimately it falls far short, morphologically, of the normal arrangement. Nevertheless, the extent to which the residual defect after delayed reinnervation is attributable to changes developing within the muscle remains uncertain. In the absence of any suitable test of function, the restrictions which are imposed on the restoration of function by these abnormal morphological

changes must remain purely inferential, and it is conceivable that patterns of reinnervation which appear abnormal histologically (excluding, of course, absence of reinnervation) may still be compatible with recovery of a useful degree. Furthermore, considerable doubt exists as to how much of the abnormality of the reinnervation pattern (experimental material) and of the residual functional defect (clinical material) is attributable to changes developing within the muscle as the result of the denervation and how much to a reduction in the number of appropriate axons reaching the muscle and to the failure of the restored pathways to maturate into functionally efficient units. Though it is certain that several factors are operating, it is important to decide the relative contribution of each. That the duration of denervation is of significance is not denied, but the point at which it becomes critical cannot be decided until it is possible to effect a separate measurement of the various factors contributing to, and complicating, the recovery.

The clinical cases which have been reviewed in this paper have provided data to the effect that some muscles, particularly those innervated at more proximal levels, recover fully, or very well, after denervation for at least 12 months. The poor recovery observed in the distal muscles after nerve suture at high levels, as opposed to the more satisfactory recovery of the proximal muscles, has been attributed by some to the longer period for which the former have been denervated. This is an unlikely explanation, for the following reasons: After an immediate or early suture the distal muscles will have been denervated for a much shorter period than the proximal muscles in a patient in whom suture has been delayed for 12 months. Despite this, the quality of the recovery distally after early or immediate suture is still inferior to that recorded for the proximal muscles after delayed repair. Other factors, however, are operating which adversely influence recovery at the periphery of the limb. Briefly, conditions are more favorable for recovery in the proximal than in the distal muscles for the following reasons:

1. The nerve fibers supplying the proximal muscles occupy a greater cross-sectional area of the nerve at the site of suture.[12]

2. They are more sharply localized in the nerve at proximal levels than the fibers destined for more distal structures.[13]

12. Sunderland, S., and Bedbrook, G. M.: The Cross-Sectional Area of Peripheral Nerve Trunks Occupied by the Fibres Representing Individual Muscular and Cutaneous Branches, Brain **72**:613, 1949.

13. (*a*) Sunderland, S.: The Intraneural Topography of the Radial, Median, and Ulnar Nerves, Brain **68**:243, 1945. (*b*) Sunderland, S., and Ray, L. J.: The Intraneural Topography of the Sciatic Nerve and Its Popliteal Divisions in Man, ibid. **71**:242, 1948.

Thus, in the competition for endoneurial tubes after high repair, the axons for the distal muscles suffer a distinct disadvantage in comparison with the fibers destined for more proximal branches in that they are fewer, whereas those of individual branches are well mixed, and not localized, in the nerve.

3. An additional factor is that the consequences of loss of axons and disorderly reinnervation are more serious for the distal than for the proximal muscles. The latter often combine as prime movers in executing movements; for this reason, the reinnervation of one member of the group by fibers originally supplying another does not seriously disturb the pattern. This assists in the restoration of function. On the other hand, the muscles controlling the digits function as independent, but well integrated and coordinated, systems in every moment, combining to give that delicacy, refinement and precision of action which, in the case of the hand, is the basis of manual dexterity. In these complex and finely adjusted movement patterns each muscle has a specific role to play. Consequently, any disturbance of the fiber pattern during the regeneration of axons to these muscles seriously impairs the restoration of function.

The complete or excellent recovery in some muscles, together with the explanation advanced to account for the poor recovery in muscles innervated in the distal part of the limb, makes it unlikely that intramuscular changes induced as a result of prolonged denervation (within the period available for investigation) could have been responsible for the residual defect in those muscles which recovered only partially. This, in turn, suggests that the factors limiting the recovery were based on the failure of axons to reach the muscle in sufficient numbers and from appropriate neurons, rather than on irreversible changes developing in the endoneurial tubes of the distal stump, the end organs and the muscle as a result of prolonged denervation.

There is, moreover, additional evidence to suggest that fewer axons had reached the permanently disabled muscles listed in tables 1 and 2. Thus, several of the nerves were injured at proximal levels by high velocity missiles which caused considerable damage, while in many patients the wounds were severely infected for long periods. Furthermore, in the cases of gunshot wounds greater lengths of nerve were destroyed, owing to the greater severity of the injury and the more extensive intraneural fibrosis induced by the trauma and infection. In these circumstances, certain effects could be expected:

1. The retrograde neuronal effects would be severer, with a high incidence of degeneration and a greater reduction in the number of surviving axons.

2. Many regenerating axons would fail to reach the funiculi and the endoneurial tubes of the distal stump owing to (*a*) the dissimilarity of the cross-sectional area of the nerve ends, consequent on denervation shrinkage of the distal stump, which increases with the period of denervation [14]; (*b*) the dissimilarity in the funicular patterns of the nerve ends, which increases with the length of nerve destroyed and resected in the preparation of the nerve ends for repair [13a]; (*c*) scarring at the suture line, which is inevitable, no matter how well the nerve is repaired, owing to the fact that even the most suitable suture materials available excite some reaction, which obstructs and deflects axons in their passage across the suture line.

3. The chances of satisfactory regeneration would be reduced, since nerve suture was effected under tension.

4. In the cases of injury at a high level the entry of axons into foreign tubes was facilitated, owing to the considerable intermingling of branch fibers which obtains at such levels. The muscles innervated by the nerve, however, are not all affected in equal degree. Thus, after repair in the proximal part of the limb, conditions are more favorable for recovery in the proximal than in the distal muscles. The reasons for this have already been outlined.

A further point which favors the interpretation that the residual motor disability is due essentially to a reduction in the number of appropriate axons reaching the muscle is that such residual defects are common after immediate and early secondary repair when denervation changes in the muscle are not a contributing factor.

In view of the several factors which combine to reduce the number of functionally useful axons which reach a muscle, it is surprising that full recovery should be recorded in some. Possible explanations for such recovery may be noted:

1. Complete recovery was never observed in any of the distal muscles, but only in the proximal. The fibers innervating proximal muscles are sharply localized in the nerve at and just above the elbow, and it is likely that the localization in the cases under review was such as to favor the restoration of correct connections during regeneration. Other factors favoring recovery in the proximal muscles have been mentioned in an earlier section.

2. The compensatory hypertrophy of satisfactorily reinnervated fibers would offset the loss of some units.

3. The muscles were recorded as normal on the basis of clinical tests, which, though exacting, did not take into consideration the

14. Sunderland, S., and Bradley, K. C.: Denervation Atrophy of the Distal Stump of a Severed Nerve, J. Comp. Neurol., to be published.

capacity of the muscle to stand up to prolonged effort. Had the muscles been tested for this, it is certain that residual defects would have appeared and that these would have represented the functional expression of an abnormal pattern of reinnervation.

SUMMARY AND CONCLUSIONS

1. It has been ascertained that complete or very good restoration of function can occur in reinnervated human muscles after denervation for at least 12 months as the result of nerve severance, providing that the axons can be directed in sufficient numbers to their original or functionally similar endoneurial tubes and end organs and that the quiescent muscle has been maintained in the best possible condition by appropriate therapy. From this it is concluded that the duration of the denervation and the changes induced in the muscle do not assume significance as regards irreversibility within the first 12 months of denervation.

2. The most potent factors responsible for the residual defect in muscle function after nerve suture are those which lead to a reduction in the number of functionally effective axons which reach the muscle. Such factors are (*a*) retrograde neuronal degeneration, which results in a reduction in the number of surviving axons; (*b*) denervation atrophy of the distal stump and the contained funiculi, which results in the failure of regenerating axons to reach the endoneurial tubes of the distal stump; (*c*) factors responsible for the erroneous cross shunting of regenerating axons, so that the latter fail to find, enter and descend along appropriate, i. e., corresponding or functionally similar, endoneurial tubes in the distal stump.

3. Additional factors which may operate below the level of the lesion are (*a*) changes developing in the muscle as a result of the denervation which may reduce the chances of restoring useful neuromuscular connections or produce a condition in individual muscle fibers which is incompatible with normal functioning after satisfactory reinnervation, and (*b*) changes in the distal stump which delay or prevent the conversion of the restored axonal pathway into a functionally efficient fiber.

The available evidence, however, suggests that these two factors do not assume significance within the first 12 months of denervation.

THE SYNDROME OF ANOSOGNOSIA

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WHILE accounts of cases of anosognosia [1] have mainly concerned descriptions of patients who have denied the existence of left hemiplegia and blindness, there have been reported many instances of denial or unawareness of other defects. Schilder,[2] Von Hagen and Ives,[3] Nielsen and Ives,[4] Nielsen,[5] Olsen and Ruby,[6] Sandifer [7] and Rosenbaum [8] recorded cases of denial of right hemiplegia. Unaware-

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1. While the term "anosognosia" was used by Babinski (Contribution à l'étude des troubles mentaux dans l'hémiplégie organique cérébrale [anosognosie], Rev. Neurol. **22**:845-848, 1914) to denote denial of left hemiplegia, it will be used in this paper to describe denial of any defect or illness.

2. Schilder, P.: Localization of the Body Image (Postural Model of the Body), A. Research Nerv. & Ment. Dis., Proc. **13**:466-484, 1932.

3. Von Hagen, K. C., and Ives, E. R.: Anosognosia (Babinski), Imperception of Hemiplegia: Report of Six Cases, One with Autopsy, Bull. Los Angeles Neurol. Soc. **2**:95-103 (Sept.) 1937.

4. Nielsen, J. M., and Ives, E. R.: Generalized Autotopognosia Due to Focal Cerebral Lesions: Its Resemblance to Finger-Agnosia, Disturbance of Right and Left and Anosognosia of Babinski, Bull. Los Angeles Neurol. Soc. **2**:155-163 (Dec.) 1937.

5. Nielsen, J. M.: Gerstmann Syndrome: Finger Agnosia, Agraphia, Confusion of Right and Left and Acalculia: Comparison of this Syndrome with Disturbance of Body Scheme Resulting from Lesions of the Right Side of the Brain, Arch. Neurol. & Psychiat. **39**:536-560 (March) 1938.

6. Olsen, E. W., and Ruby, C.: Anosognosia and Autotopognosia, Arch. Neurol. & Psychiat. **46**:340-344 (Aug.) 1941.

7. Sandifer, P. H.: Anosognosia and Disorders of Body Scheme, Brain **69**:122-137 (June) 1946.

8. Rosenbaum, M.: "Pentothal Sodium" as an Adjunct in Therapy of Anxiety Hysteria: Report of a Case, Arch. Neurol. & Psychiat. **60**:70-76 (July) 1948.

ness of paraplegia was reported by Stengel and Steele.[9] Roth [10] observed anosognosia for hemiballismus. There are also cases of denial of alexia,[11] auditory agnosia [10] and deafness.[12] Fulton and Bailey,[13] Nielsen and Raney,[14] and Redlich and Dorsey [15] observed patients who denied that they were ill at all or that they had been operated on. Most of the discussion has centered about whether a focal lesion can produce anosognosia or whether diffuse involvement of the brain is necessary. The problem also exists as to whether anosognosia can occur as an isolated entity or whether it always appears as part of a more generalized defect. In considering the mechanism of anosognosia, comparatively little observation of the total behavior of the patients over a period of time has been carried out. Many authors have focused attention on the anosognosic delusion and have ignored other aspects of dysfunction. Though disturbances of consciousness are discussed, few electroencephalographic records are available. The importance of premorbid personality has been mentioned by Sandifer,[7] Wortis and Dattner,[16] Roth [17] and Rosenbaum [8] but has not been studied systematically. In only one recorded instance has there been an attempt to produce the phenomenon experimentally,[18] although denial of operation has been reported in patients after prefrontal lobotomy [19] and prefrontal lobectomy.[20] The present study of 22 patients with brain tumor and various types of anosognosia indicates the importance of more comprehensive methods of study.

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9. Stengel, E., and Steele, A. D. F.: Unawareness of Physical Disability (Anosognosia), J. Ment. Sc. **92**:379-388 (April) 1946.

10. Roth, N.: Unusual Types of Anosognosia and Their Relation to the Body Image, J. Nerv. & Ment. Dis. **100**:35-43 (July) 1944.

11. Bonhoeffer, K.: Casuistische Beiträge zur Aphasielehre, Arch. f. Psychiat. **37**:564, 1903.

12. Anton, G.: Über Herderkrankugen des Gehirns, welche vom Patienten selbst nicht wahrgenommen werden, Wien. klin. Wchnschr **11**:227-229, 1898.

13. Fulton, J. F., and Bailey, P.: Tumors in the Region of the Third Ventricle: Their Diagnosis and Relation to Pathological Sleep, J. Nerv. & Ment. Dis. **69**:1 (Jan.); 145 (Feb.); 261 (March) 1929.

14. Nielsen, J. M., and Raney, R. B.: Symptomatology of Tumors of the Third Ventricle, Bull. Los Angeles Neurol. Soc. **4**:1-7 (March) 1939.

15. Redlich, F. C., and Dorsey, J. F.: Denial of Blindness by Patients with Cerebral Disease, Arch. Neurol. & Psychiat. **53**:407-417 (June) 1945.

16. Wortis, H., and Dattner, B.: An Analysis of a Somatic Delusion: A Case Report, Psychosom. Med. **4**:319-323 (July) 1942.

17. Roth, M.: Disorders of the Body Image Caused by Lesions of the Right Parietal Lobe, Brain **72**:89-111 (March) 1949.

18. Hoff, H., and Pötzl, O.: Experimental Nachbildung von Anosognosie, Ztschr. f. d. ges. Neurol. u. Psychiat. **137**:722-734, 1931.

19. Freeman, W., and Watts, J. W.: Prefrontal Lobotomy: Convalescent Care and Aid to Rehabilitation, Am. J. Psychiat. **99**:798-806 (May) 1943.

20. Peyton, W. T.; Haavik, J. E., and Schiele, B. C.: Prefrontal Lobectomy in Schizophrenia, Arch. Neurol. & Psychiat. **62**:560-571 (Nov.) 1949.

OBSERVATIONS

The clinical, neurological and pathological data are indicated in the accompanying table, while disturbances of behavior are described in detail. The lesions were located in the frontal, temporal and parietal lobes and the diencephalon, midbrain and posterior fossa. In 4 cases postmortem examination of the brain was made. In 11 cases the diagnosis of tumor was verified at craniotomy, while in 7 instances the diagnosis of neoplasm was made on the basis of clinical and roentgenographic evidence. Of the surgically verified cases, the complete extent of the lesion could be determined only in the 2 cases of acoustic neurinoma. In 16 cases there was increased intracranial pressure; in 10 there was bloody or xanthochromic cerebrospinal fluid. In 4 instances the lesions were putatively of metastatic origin. In the 5 cases (9, 10, 11, 12 and 16) with normal intracranial pressure and clear or only faintly xanthochromic spinal fluid, the tumors were bilateral and involved the region of the third and lateral ventricles. In 9 instances (cases 2, 3, 7, 8, 13, 15, 17, 20 and 21) the anosognosia appeared after craniotomy, while in one (case 19) it was noted after a grand mal convulsion.

Electroencephalographic records were made in 17 cases; in 16 they showed bilateral abnormalities with appearance of delta activity, of frequencies ranging from 1 to 7 per second. In some cases there was focal accentuation over the region of the neoplasm, but in no instance was anosognosia associated with only a focal, unilateral electroencephalographic disturbance. In one instance (case 2), there was diffuse activity during the period of anosognosia, but after the disappearance of the anosognosia abnormal waves were localized to the site of the actual lesion. When the anosognosia recurred, there was again bilateral abnormality in the electroencephalographic record.

The types of anosognosia observed included nonrecognition and denial of the following aspects of disease: urinary and fecal incontinence, sexual impotence, left hemiplegia, right hemiplegia, vomiting, blindness, involuntary movements, loss of memory and the fact that an operation had been performed or that the patient was ill. In all cases the anosognosia involved more than a single defect. A number of general patterns were observed. First, the patient might state that he was perfectly well and deny any sign or symptom of illness. Second, the patient might deny the major disability but lay stress on some trivial aspect of his condition, a form of displacement. Thus, a woman (case 5) with paralysis of the right leg and inability to walk ignored these defects but complained bitterly about constipation. After craniotomy, a patient denied having had an operation on his head but admitted that one had been performed on his foot, where he had had a cut-down on a vein. Third, the patient might express some awareness of illness but attribute the manifestations

to a benign cause. One man (case 8), after a suboccipital craniotomy, denied having had an operation and stated that the bandages had been placed on his neck and head because of a sore throat. A patient with left hemiplegia said she could move her limbs but was too lazy to do it. Or the patient might express awareness of the defect but rationalize or minimize it to the point where it was not regarded as a defect. One patient (case 17) admitted that she wet the bed but insisted that "everybody did it." Fourth, the patient might project the defect onto some one else. Thus, a patient denied that the paralyzed limbs were her own and claimed that they belonged to the nurse. Another, with a cholesteatoma of the third ventricle (case 9), when questioned about her ailment, answered that she was perfectly well but that her daughters were sick and should be examined. Finally, a patient might state that the defects existed in the past but that he was well at present.

Various methods of denying or explaining away the defect might be used by the same patient at different times and were even observed in a single interview. Thus, one patient (case 9) first denied having urinated in bed, then attributed the wet bed to the dampness outside and finally accused the examiner of having wet the bed. Contradictory statements might also be made, as in the instance of a patient (case 3) who denied having had a craniotomy but complained about the sawing and hammering that had been done on his head.

Confabulations occurred in each case. They usually were not offered spontaneously but could be elicited in answer to a question about the patient's health or activities. Three general types of confabulation could be distinguished. In the first, the patient would deny the defect completely, and the confabulation would explain the obvious appearance of illness. Thus, a patient (case 8) explained that he was in the hospital because he now was employed there as a "stationary engineer." The second type of confabulations involved accounts of supposed events or accomplishments which in themselves were incompatible with a serious illness. Thus, patients would relate how they had gone home or had been to the movies. Patients unable to leave the bed described having gone for a walk. Two patients (cases 10 and 11) who were impotent told of having had sexual relations. Even when a defect might be admitted on direct questioning, the confabulation would express the denial of illness. A patient with a chiasmal lesion (case 12) would admit at times that he was blind after repeated questioning, but he would then confabulate about reading the newspapers and going to the movies. On one occasion he stated that the reason he was in the hospital was that, while on his way to the store "to buy butter and eggs," he had been forcibly seized, brought to the hospital and placed in bed. The third type of confabulation, observed less frequently than the others, did not deal directly with the denial of the overt defect but was, rather, related to what the patient felt

Case No.	Patient, Sex, Age	Lesion	Neurological Findings	Spinal Fluid	Electroencephalogram	Anosognosia
1	A. P. F 47	Spongioblastoma in right frontal lobe, extending deep to third ventricle; operation	Papilledema; staggering gait; urinary and fecal incontinence	Xanthochromic; pressure 280 mm. of water; total protein 100 mg./100 cc.	Diffuse delta activity; frequency 1-6 per sec., mainly in left frontal region	Operation; incontinence; illness
2	J. D. M 47	Metastatic adenocarcinoma in right frontoparietal region; operation	Papilledema; left hyperreflexia and Babinski sign; urinary incontinence	Clear; pressure 180 mm. of water; total protein, 49 mg./100 cc.	Diffuse delta activity; frequency 1-4 per sec., mainly from right inferior frontal electrode	Operation; incontinence
3	M. W. M 33	Chromophobe adenoma of pituitary; operation	Homonymous defect in lower right quadrant of visual fields; history of sexual impotence	Bloody after operation; pressure 260 mm. of water	Diffuse delta activity; 6 per sec.	Operation; impotence
4	J. P. M 29	Chorioepithelioma of third ventricle invading right thalamus and internal capsule; operation; autopsy	Polyuria; polydipsia; bitemporal hemianopsia; blindness following craniotomy	Xanthochromic; pressure 105 mm. of water; total protein 180 mg./100 cc.	Diffuse 3-6 per sec. activity	Blindness; operation
5	P. S. F 42	Piloid astrocytoma involving thalami, basal ganglia and corpus callosum; autopsy	Paralysis right leg; paresis right arm; involuntary movements of right leg; dystaxia of right arm; urinary and fecal incontinence	Clear; pressure 140-180 mm. of water; up to 215 lymphocytes per cu. mm.	Diffuse 4-6 per sec. activity	Incontinence; involuntary movements and paralysis of right leg; paresis of right arm
6	B. A. F 28	Glioma obliterating third ventricle, extending from posterior commissure to optic chiasm into median nuclei of thalamus; lateral ventricles enlarged; aqueduct displaced; autopsy	Nystagmus; paralysis of right conjugate gaze; bilateral ataxia; urinary incontinence	Clear; pressure 185 mm. of water; total protein 100 mg./100 cc.	Not recorded	Illness; incontinence
7	F. M. F 38	Spongioblastoma of right temporal lobe; operation	Papilledema; left hemiplegia; urinary incontinence	Clear; pressure 280 mm. of water; total protein 41 mg./100 cc.	Diffuse delta activity with slowest frequency at frontal electrodes particularly on right	Left hemiplegia; operation
8	W. J. M 51	Intracranial metastases; mass in chest shown roentgenographically; dilatation of lateral and third ventricles in ventriculogram; no lesion apparent on exploration of posterior fossa	Papilledema; ataxic gait; urinary incontinence	Clear; ventricular fluid under increased pressure	Symmetrical diffuse 2-6 per sec. activity	Operation; incontinence; vomiting; memory loss; illness
9	L. T. F 61	Cholesteatoma of third ventricle extending to infiltrate right thalamus, basal ganglia and internal capsule; operation; autopsy	Bilateral optic atrophy; pupils sluggish to light; staggering gait; bilateral Babinski sign; urinary incontinence	Faintly xanthochromic; pressure 120 mm. of water	Diffuse symmetrical 3-6 per sec. activity	Illness; incontinence
10	S. D. M 44	Filling defect of third ventricle with elevation of floor of body of right lateral ventricle shown in pneumoencephalogram	History of impotence; urinary incontinence	Clear; pressure 130 mm. of water; total protein 53 mg./100 cc.	Diffuse symmetrical 5-6 per sec. activity	Impotence; incontinence; memory loss

11	E. F. M 24	Chromophobe adenoma (?) of pituitary; enlarged, eroded sella apparent in roentgenogram	Polyuria; polydipsia; history of impotence; optic atrophy; bitemporal hemianopsia, followed by blindness; paralysis of upward gaze; loss of pupillary reaction to light; bilateral Babinski sign; urinary incontinence	Clear; pressure 80 mm. of water; total protein 111 mg./100 cc.	Not recorded	Blindness; impotence
12	J. d'A. M 32	Tumor of third ventricle (?); mass intruding into mesial wall of left lateral ventricle shown in pneumoencephalogram; neoplasm not disclosed at craniotomy	Polyuria; polydipsia; bitemporal hemianopsia, followed by blindness; pupils fixed to light	Clear; pressure 110 mm. of water; total protein 200 mg./100 cc.	Diffuse 6-7 per sec. activity	Blindness; operation
13	W. McL. M 52	Acoustic neurinoma; cyst adherent to cerebellum; operation	Ataxic gait; nystagmus; deafness in right ear; anesthesia of right cornea	Clear; ventricular fluid under increased pressure	Not recorded	Operation; memory loss
14	R. M. M 48	Cholesteatoma of lateral ventricles; operation	Left hemiparesis; urinary incontinence	Xanthochromic; pressure 110 mm. of water	Diffuse 4-6 per sec. activity	Operation; incontinence; left hemiparesis
15	C. S. F 42	Neoplasm of midbrain (?); dilatation and asymmetry of lateral and third ventricles and displacement to left of caudal part of third ventricle shown in ventriculogram; no tumor revealed on exploration of posterior fossa	Papilledema; paresis of upward gaze; rigidity of all extremities; urinary incontinence	Xanthochromic; pressure 380 mm. of water	Diffuse symmetrical 3-6 per sec. activity	Operation; incontinence
16	S. L. M 58	Chromophobe adenoma of pituitary; operation	Optic atrophy; bitemporal hemianopsia; blindness; urinary and fecal incontinence	Clear; pressure 110 mm. of water; total protein 95 mg./100 cc.	Not recorded	Operation; blindness
17	M. S. F 47	Sarcoma of left orbit invading anterior fossa; operation	No preoperative symptoms; incontinence of urine after operation	Bloody after operation	1-2 per sec. delta activity over both frontal areas	Incontinence; operation
18	P. K. M 59	Transitional glioma of left frontal lobe; operation	Ataxic gait; papilledema; bilateral Babinski sign; urinary incontinence	Xanthochromic; pressure 230 mm. of water; total protein 280 mg./100 cc.	Normal record	Operation; illness
19	I. F. F 41	Intracranial (?) metastasis from adenocarcinoma of sigmoid (laparotomy)	Grand mal convulsion; slight left hemiparesis	Clear; pressure 170 mm. of water; total protein 78 mg./100 cc.	Diffuse 6-7 per sec. delta activity	Operation; illness
20	G. B. M 56	Acoustic neurinoma; operation	Ataxic gait; nystagmus; deafness in right ear; absence of right corneal reflex; urinary incontinence	Clear; pressure 180 mm. of water; total protein 240 mg./100 cc.	Not recorded	Operation; incontinence
21	B. E. M 53	Ependymoma of right lateral ventricle; operation	Papilledema; ataxic gait; urinary incontinence	Bloody after operation	Diffuse 4-6 per sec. delta activity	Operation; incontinence
22	B. S. F 40	Vascular anomaly of right temporoparietal lobe; pineal shift shown in angiogram	Left hemiparesis; left homonymous hemianopsia; papilledema; retinal hemorrhage	Xanthochromic; pressure 120 mm. of water	Diffuse 6 per sec. delta activity	Illness; memory defect

was an inadequacy in his life situation. Thus, one man (case 13), an accountant of mediocre talents, boasted that he was the best tax lawyer in the city and had written half the books on the subject. Other confabulations were paranoid formations directed against the spouse, who was described as engaging in some sort of hostile or immoral activity.

Disorientation for place was present in 19 of the 22 cases. The patient might state that he was home or in a hotel or in some other place removed from a hospital. Most patients said they were in a hospital but frequently gave it another name. Or the hospital might be named correctly but be displaced to another part of the city or another city, generally closer to the patient's home. One patient (case 2) located the hospital in Bridgeport and said that his home was across the street. Another (case 14) said that the hospital and his home were actually in the same building, explaining that both were now part of a housing project. Types of temporal displacement also appeared. Thus, one patient located the hospital at the address of the physician where she had been prior to her admission. Condensations were used. One patient remarked that he was in "Mount Sinai restaurant," while another was in "Mount Sinai University." Patients who said that they were not in a hospital appeared to establish the faulty orientation by using certain details of the environment. Thus, a woman (case 5) said she was in a bank because she noted a locked medicine cabinet, while another (case 15) with severe vertigo said she was on a ship. At the same time, these patients identified doctors and nurses, accepted medication with equanimity and explained the discrepancy with some rationalization or confabulation.

Temporal disorientation was present in all 22 cases and usually persisted after orientation for place had returned. In all instances there was difficulty in determining the time of day. This was brought to our attention early, when patients would repeatedly ask the nurse what time it was. Despite opportunities to look out of the window, observe ward activities and even see a large wall clock, they would be confused between morning and afternoon, and even between day and night. It is significant that in several cases the first abnormalities of behavior noted involved this type of temporal disorientation. One patient (case 1) came home from work and took a nap. On awakening at 9 p. m., she thought it was morning and she was late for work. She telephoned her office and became angry at the operator because there was no answer. She dressed and went as far as the subway before she realized her mistake. Another woman, examined in the morning, would say it was 7 : 00 in the evening because she was expecting her daughter, who always came at that hour. It appeared that in many instances the patient was judging the time in terms of his own experience and disregarding the clues in the external environment. These experiences were mainly those relating to sleeping

and meals. Some patients were less likely to make errors when asked the time during or just after eating. One man (case 3), when asked the time after awakening from his afternoon nap, would reply that it was 3:00 or 4:00 in the morning. Attempts to point out his error were unsuccessful. He maintained that it must be morning because he had awakened shortly before and he never slept in the afternoon. Errors were also made in determination of the year and month, but these were not as constant as disorientation for time of day. When the year was given incorrectly, an earlier date was invariably named.

In most patients there was an over-all reduction in spontaneity and initiative. When sought for an interview, patients were often found lying on their beds with their eyes closed. However, they responded promptly to questions and seemed alert during the examination. Although the patients slept more, it was only with the severer impairments of function that actual drowsiness was noted. In these patients lethargy might alternate with periods of hyperactivity, and even hypomanic behavior. In the stages of hyperactivity patients would try to get out of bed, attempt to leave the ward or pick at their dressings. In 5 cases stereotyped mannerisms were observed. Urinary incontinence was present in 16 cases and denied in 12. Fecal incontinence occurred in 4 cases.

Nearly all the patients showed some form of language disturbance. Mainly, there was a paraphasia in which objects were referred to in terms of some single physical or functional characteristic. Thus, a fountain pen was called a "pencil" by some patients and an "underwater pen" by another. A wallet was called a "portfolio." The hospital was called a "place for rest and relaxation." Language in general was banal, with many clichés. In the cases with the severest involvement, condensations and neologisms were used.

Evidences of auditory and visual hallucinations were observed in 10 cases. In certain cases a direct relation between the content of the hallucination and the patient's illness could be determined. Thus, a man with impotence and blindness in association with a pituitary adenoma (case 12) would lean out of bed and call to his dog, "Penny." He also maintained that his wife was under the bed having a baby. A patient with paralysis of the right lower extremity and paresis of the right upper limb told the nurse that she had lost her right leg and she wondered what was going to be done about finding it. The next day she became very agitated and said that she had seen her right leg and part of her right arm on her bedside table, "just like you would put false teeth on the table."

Changes in affect were striking. Fifteen of the patients were euphoric or manifested an air of serenity and bland unconcern. This cheerful demeanor fitted the affirmation of health. A type of "gallows humor"

could be detected in the patient who referred to his operation for "acoustic aroma" and in another who identified the hospital as "Mount Cyanide." In 4 patients (cases 1, 5, 6 and 13) there was pronounced depression in the earlier stages of the illness. As the defects became severer and disorientation developed, the emotional depression was replaced by euphoria. Also, in several instances, notably case 14, improvement in sensorium and orientation was associated with awareness of illness and depression. In rare instances, by persistent questioning, a patient could temporarily be brought to admit his defect. In 6 of the cases of euphoria there were transient episodes of paranoid delusions, while in 4 (cases 7, 10, 11 and 12) the prevailing mood was paranoid. The formulations were mainly concerned with attributing the manifestations of illness to the activities of others. It was common for a patient with urinary incontinence to charge that the nurse or doctor had wet his bed. It appeared as though the problem of illness could be solved by denying it or blaming some one else.

From a study of our patients, and of others with tumors and vascular disease of the brain, it appears that the occurrence of anosognosia is related to the pattern of the premorbid personality. These data will be presented in another communication and have been omitted from the case reports, but several observations may be noted. Almost all patients who showed disturbance of orientation, language, psychomotor activity and affect of the type described had some manifestation of anosognosia. The patients in whom it developed most strikingly had in their background considerable insecurity and a strong drive to perfection and superiority. They had apparently regarded illness as an imperfection and had reacted with guilt or anxiety. The patients who exhibited euphoria were described as having been compulsive, meticulous and worrisome. Those who became paranoid had shown a more overt type of hostility. It appeared as though the anosognosic delusion formed a part of an altered pattern of interpersonal relations, which, like the disturbances in orientation and language, represented a restriction in the patient's contact with the environment.

Some defect of memory and retention was found in all the patients. However, the degree of impairment was extremely variable, and the anosognosia could not be accounted for on the basis of defective memory. One patient (case 3) showed an extremely slight memory defect, as demonstrable on routine tests, but persistently denied that any operation had been performed. Great variability could be shown in other respects. Patients who could retain 8 digits forward and 4 backward could not remember the names of their doctors. One patient (case 17) could repeat 8 digits forward but none backward. None of the patients could do serial subtractions of 7's from 100 accurately. There was no particular relation between the loss of recent and of remote memory. Thus, patients

who could not remember whether they had eaten lunch could give accurate details of their past life. Another, however, could not remember whether he was married or not, and one man did not recall being a Mason, although he had been one for 21 years.

It was noted that the disturbed behavior in many instances was accentuated by the administration of barbiturates for sedation. After the disappearance of the anosognosia and the return of complete orientation in 3 patients (cases 3, 14 and 21), amobarbital sodium (sodium amytal®) was given intravenously to the point where nystagmus, slurring of speech and difficulty in counting backward appeared. At this stage, which occurred after injection of 3 to 5 grains (0.195 to 0.325 Gm.) of the drug, denial of illness and operation, with disorientation and confabulation, returned. Following this procedure, there was complete amnesia for the entire interview and the patient was again oriented and admitted his defects.

REPORTS OF CASES

CASE 7.—F. M., a housewife aged 38, was admitted to the hospital on March 14, 1949, because of severe headache and change in behavior. Since the birth of her child, four years before, she had complained of weakness and fatigue. One year before admission she had had a "spell," lasting for about an hour, in which she appeared to be asleep and could not be roused. A second such attack, accompanied with twitching of the mouth, occurred a month later. She then began to complain of dizziness and a feeling of pressure in her head. These symptoms were attributed to emotional tension, and under psychiatric treatment the patient showed some improvement. Five weeks before her admission severe headaches and vomiting developed and a change in behavior was noted. The patient became forgetful. She would go to the store, but then return because she could not remember what she wanted. One day her husband found their younger child playing with razor blades, while the patient, hitherto a devoted and worrisome mother, looked on with apparent unconcern. In general, the patient seemed to be easy-going and relaxed, in contrast to her former compulsive behavior. In the several days preceding admission she had become incontinent of urine.

Examination showed the patient to be drowsy, but she could be easily aroused. There was slight left hemiparesis with increased deep reflexes and an extensor type of plantar response on the left. Papilledema was noted in the right fundus. Lumbar puncture yielded clear fluid under an initial pressure of 280 mm. of water, with a total protein content of 41 mg. per 100 cc. There were tenderness to pressure in the left temporal region and dilated veins over this area. An electroencephalogram showed a large amount of diffuse delta activity, with the slowest frequency appearing at the frontal electrodes, particularly on the right. Four days after admission the patient had a clonic convulsion involving the left limb. She was incontinent of urine and was disoriented for the time of day, frequently asking the nurses the day and hour. On March 21 a craniotomy was performed by Dr. Benno Schlesinger. Resistance to the exploratory cannula was encountered in the right temporal lobe at a depth of 3 cm., and a dark bluish vascular tumor was exposed on the floor of the temporal fossa. On histological section this proved to be a spongioblastoma. After the operation, there were complete paralysis of the left upper extremity and pronounced paresis of the left lower extremity, with occasional clonic jerkings of the left limbs.

Two days after operation the patient was noted to sleep most of the day but she could be aroused easily for examination. She was able to perceive touch, pinprick, pressure and vibratory stimuli in the left limbs. Two point discrimination and position sense were impaired, and she had difficulty in telling which finger of her left hand was being held. The patient denied there was anything the matter with her left arm or leg. When asked to raise her left arm, she repeatedly raised her left leg. When this error was pointed out to her, she said, "Oh, some people call it an arm; some a leg. What's the difference!" On other occasions she would raise her right arm when asked to move the left. When asked to distinguish between her right arm and left leg, she could do so without difficulty. When the examiner raised the patient's left arm and asked her to identify it, she stated that it was his arm. On other occasions the patient stated that the paralyzed left arm belonged to the nurse. The patient also denied that an operation had been performed. Even when she was shown her shaven head and the operative wound in a mirror, she still refused to admit that an operation had been performed. She would become irritable when asked about an operation, saying, "It's ridiculous. Why, an operation would be the last thing." She complained to her husband, "Why are people bothering me about a nonexistent operation?" She continued to be incontinent of urine but would not deny this when questioned. On one occasion when she was incontinent of feces, she did deny it, saying it must have been some one else. Confabulations were not prominent. On one occasion she said she had been out of bed for a walk, and at another time, that she had been home.

The patient remained well oriented for place. She also knew the date but was consistently disoriented for the time of day. She would repeatedly ask the nurses what time it was, usually thinking it was later than it actually was. One afternoon during visiting hours she asked the time and, on being told it was 3:30, exclaimed, "What are all these people doing here at 3:00 in the morning?" There were disturbances in language. The patient misnamed objects in paraphasic fashion. She called a thermometer a "gradient" and a wallet a "portfolio." She referred to herself as "he" or "they" and alluded to her left arm as "he." When examined on March 29, eight days after operation, she could repeat 4 digits forward and 2 backward, but she could not recall the names of any of her nurses or doctors. She remembered the events of the previous day but did not recall having had a lumbar puncture. She was able to remember all the visitors she had had that day except her husband.

The patient's mood was paranoid and irascible. At times she would accuse the examiner of trying "to drive me crazy." She was sardonically humorous, referring to the hospital as "Mount Cyanide." She complained that she was weak and confined to bed because she was not fed properly. On one occasion she accused the nurses of trying to poison her and stated that she was forcibly being kept in the hospital. She was especially bitter toward her husband, whom she accused of trying to have her confined to a mental institution. She became concerned with sexual matters. Once she tried to fondle the nurse's breasts and accompanied this with vulgar remarks. She warned the examiner not to make any sexual advances toward her, as she was "very strait-laced." She developed the transient delusion that the patient in the next bed had gone up to the operating room as a woman but had come down a man. After roentgenotherapy was begun on April 1, the patient charged that the treatment was giving her cancer.

Power in the left extremities improved so that on March 29, nine days after operation, the patient was able to move the fingers of her left hand. At this time she admitted that the left arm was weak and that it belonged to her, but she still

denied having been operated on. Along with this, however, she would talk and joke about her "bulge," referring to the decompression area. She was discharged to another hospital for care as a chronic patient, on April 25. At that time she was still disoriented for time of day. She stated that she had a cancer but denied that she had had an operation.

Comment.—This case illustrates the denial of multiple defects, the temporal disorientation, a paraphasic language disturbance, the type of memory defect encountered and the development of a paranoid state as part of a change in behavior. Prior to coming to the hospital, the patient had expressed a great fear of having to have an operation: "It will make me soft brained, and I'll end up in an asylum."

CASE 4.—J. P., an unmarried lithographer aged 22, was admitted to the hospital on Aug. 24, 1947. For the past three months he had been drinking increased quantities of water and passing large amounts of urine. For two months blurred vision had been noted, and headache had commenced two days before his admission. Neurological examination revealed a bitemporal visual field defect for color, but the patient could still detect movement in the affected areas. Vision was 20/100 in the left eye and 20/200 in the right eye. By September 1 the bitemporal field defect included both movement and color. A roentgenogram of the skull was normal. Lumbar puncture yielded a xanthochromic fluid under an initial pressure of 105 mm. of water and containing 204 mg. of total protein per 100 cc. On August 28 an arteriogram was obtained by injection through the exposed left common carotid artery. This showed no abnormality. An electroencephalogram, on September 2, showed a large amount of diffuse, bilaterally symmetrical 3 to 6 per second activity without focal accentuation. After the arteriographic study, the patient's speech became slightly slurred, and a spiking fever developed. Vision also became worse.

On admission the patient responded well to questions and showed no obvious mental abnormalities. Within the next few days there appeared periods of lethargy and restlessness. He would get out of bed and attempt to leave the ward. There were periods of disorientation in which he thought he was in an English hospital, in "Memorial Hospital" or in "St. Mary's Hospital." He was disoriented for time of day and gave the date as February 1946. On September 4 he had a visual hallucination in which he saw "cops and robbers" in the right field of vision.

The patient's condition limited formal preoperative testing. On the Rorschach test he gave relatively few responses (12), of which the majority were whole responses. There was excellent integration of the component areas of the cards. All the responses corresponded accurately to the form of the card. The only disturbance in intellectual functioning was noted in the facetious remark with which he greeted card IV, "We come to those ink blots now."

On September 6, a craniotomy was performed. Through a right transfrontal approach the chiasmal region was exposed, but a neoplasm was not found. After the procedure, the patient appeared to be blind. He groped for objects in front of him and hit them with his hands. The pupils reacted in accommodation but constricted very sluggishly to light. Lumbar puncture on September 9 yielded a clear yellow fluid under an initial pressure of 300 mm. of water. Two days later the initial pressure was 120 mm.

When the patient was interviewed three days after operation, he denied that any operation had been performed, stated that he was not ill and claimed that he

was able to see. He thought that the doctors would operate on him and said he had been moved from Flushing Hospital because there was no neurosurgeon there. He confabulated, saying that he had just seen his grandmother in the ward and that she had been reading. He also told of having spoken to his mother a few minutes previously, although the mother had not been in the hospital. During

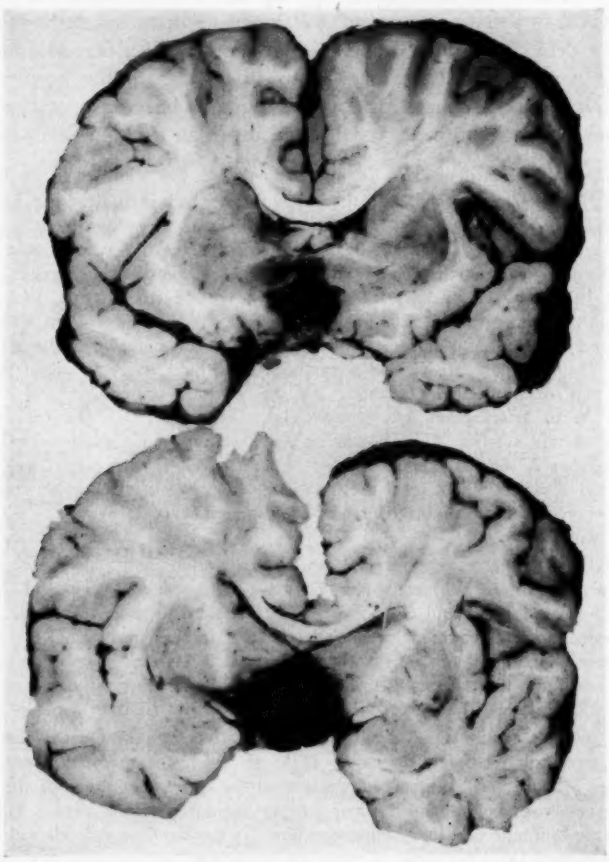

Fig. 1 (case 4).—Frontal sections of the brain showing the extent of the tumor.

the next few days the patient thought that he was in an army hospital and that he was in a machine gun unit which was about to go overseas. He became drowsier and periodically hyperactive. He developed a mannerism of spitting in his left palm and rubbing it on his right wrist. He was disoriented for time, insisting one morning that it was 3:00 in the afternoon because he had already had two meals. He continued to be disoriented for place, stating that at one time he was home in B. and on other occasions that he was in a small private hospital in India. When asked

where in India, he replied, "Asia Minor." Language included condensations and neologisms. He talked of how the other men in the ward were saying that they were "bombigators" (apparently a condensation of "bombardier" and "navigator") and that as soon as his head was fixed up he would be one, too. On being found trying to get out of bed one day, he said that he was going to get an "eye eradicator."

Complete memory tests could not be made. The patient was able to repeat 6 digits forward and 3 backward but usually could not remember when he had had his last meal. His mood became paranoid and irritable, and he would accuse the ward attendants of withholding his meals from him. The patient became steadily more somnolent and hyperactive and died on September 14.

Postmortem examination of the brain revealed a large mass completely filling the third ventricle. It was inseparable from the underlying tuber cinereum, and on the right side it had infiltrated into the thalamus and part of the internal capsule. Rostrally, the tumor extended to the level of the anterior commissure, which was softened. The lateral ventricles were elevated and reduced to narrow slits, with (some) dilatation of their most rostral ends. Caudally, the tumor extended to the aqueduct of Sylvius. Grossly, the tumor was reddish brown and mottled (fig. 1). Histologically, there were large blood sinuses invaded by villous cellular projections. The posterior lobe of the pituitary gland was also invaded by tumor cells. A diagnosis of chorioepithelioma was made.

Comment.—This case of anosognosia for blindness and denial of operation and illness is an example of a severe disturbance in orientation, psychomotor activity and language.

CASE 6.—B. A., a housewife aged 28, was admitted to the hospital on Sept. 8, 1937. Six months prior to admission, after a head cold, she began to eat poorly, complained of nausea and seemed irritable and anxious. One month previously, she began to vomit; her gait became ataxic, and she complained of headache and blurred vision. On examination, gait was unsteady, and the patient veered to the left. The head and eyes were deviated to the left, and there was paralysis of conjugate gaze to the right. Nystagmus was noted on both vertical and horizontal gaze and on fixation. The right pupil reacted sluggishly both directly and consensually to light stimuli. There were dysdiadokokinesis and dystaxia of the right upper extremity. Hearing was reduced in the right ear, and there was weakness of the right side of the face. Lumbar puncture yielded a clear fluid under a pressure of 70 mm. of water, with a total protein content of 100 mg. per 100 cc. The patient was emotionally depressed and spoke of suicide but was oriented and showed no gross memory defect. A diagnosis of an infiltrating lesion of the brain stem was made and roentgen therapy instituted. The patient improved, walked better and no longer complained of headache and blurred vision. She was discharged on November 3.

The patient was readmitted on November 19. She appeared dull and apathetic and was incontinent of urine and feces. She knew that she was in the hospital and did not believe she had ever left it. In addition to the neurological abnormalities noted on the first admission, there were now rigidity of all limbs and blurring of the optic disks. The spinal fluid pressure was 240 mm. After a week in the hospital, the patient became extremely euphoric and garrulous. However, unless spoken to, she would usually sleep. She was grossly disoriented, believing that she was home or in a restaurant or a hotel. At times she thought she was in a hospital on Second Avenue. She denied being ill or having anything wrong with her and confabulated freely. She would describe automobile trips which she had taken.

She denied being incontinent of urine and feces and said some one else had soiled her bed. She was oriented for the month and year but could not tell the time of day, usually confusing morning and afternoon. There were marked defects in calculation and memory. In the euphoric state there were paranoid episodes, in which she would accuse her family of not visiting her and berate her husband for spending all his time in the "ladies' room." When questioned about the latter statement, she denied having made it and attributed the remark to the examiner. There were pronounced language disturbances and errors in naming objects. She called a coin a "watch" and a sleeve a "buckle." When a pocket flashlight was shown her, she called it a "fountain used for reading."

The patient's condition steadily worsened, and on February 2 she was unresponsive. Lumbar puncture yielded xanthochromic fluid, under an initial pressure of 360 mm. of water, with a total protein content of 257 mg. per 100 cc. She

Fig. 2 (case 6).—Frontal section of the brain, showing the rostral part of the tumor.

picked at the bedclothes, rubbed her nose and had repetitive jerking movements of the extremities. She died on February 14.

Postmortem examination of the brain showed flattening of the convolutions and a medullary pressure cone. There was severe internal hydrocephalus of the lateral ventricles, distorting them asymmetrically. The third ventricle was almost obliterated and pushed to the left, and the aqueduct of Sylvius was slightly displaced. The tumor was infiltrating, without clear demarcation from the rest of the brain. It extended from the optic chiasm to the level of the posterior commissure, destroying the hypothalamus and invading the thalamus, particularly the medial nuclei. The entire right thalamus was swollen. There was a cystic area, 1.0 by 0.5 cm., in the interpeduncular space between the mammillary bodies and the infundibulum (fig. 2). Histological sections revealed tumor cells arranged in densely packed, lobulated strands, with mitotic figures. A diagnosis of spongio-

blastic ependymoma was made. In sections of the midbrain there was lymphocytic infiltration in the region of the substantia nigra. The brain tissue adjacent to the tumor showed severe changes. Ameboid glia were present; the vessels had thickened walls and perivascular cuffings, and nerve cells were degenerated.

Comment.—The case illustrates the change from depression and awareness of illness to euphoria and denial of illness. This paralleled the increased damage to the brain, as indicated by progression of the neurological signs, the elevation of increased intracranial pressure and the appearance of disorientation and severe language disturbance.

COMMENT

The findings indicate that tumors of various types and in various locations can produce the dysfunction of the brain in which the syndrome of anosognosia may appear. Because of the distortion of the brain which results from a neoplasm and the changes in areas removed from the tumor itself, no exact correlation between damaged structures and the dynamics of disturbed behavior could be made. Anosognosia for left hemiplegia and that for blindness have been explained on the basis of a focal lesion in the cortex, thalamus or thalamocortical connections.[21] In the case of anosognosia for left hemiplegia, it has been considered that there is disruption or fragmentation of the "body scheme," so that awareness of the left limbs and/or their paralysis is lost.[22] However, it would be difficult to account for all the numerous and seemingly diverse types of anosognosia solely on this basis. We have seen a number of patients with hemiplegia who showed disturbance of the "body scheme" with right-left disorientation, finger agnosia and sensory displacement and extinction who did not deny the hemiplegia. We and others [23] have

21. (*a*) Pick, A.: Beiträge zur Pathologie und pathologischen Anatomie des Centralnervensystems mit Bemerkungen zur normalen Anatomie desselben, Berlin, S. Karger, 1898. (*b*) Pötzl, O.: Über Störungen der Selbstwahrnehmung bei linksseitiger Hemiplegie, Ztschr. f. d. ges. Neurol. u. Psychiat. **93**:117-168, 1924. (*c*) Barkman, A.: De l'anosognosie dans l'hémiplégie cérébrale: Contribution clinique à l'étude de ce symptome, Acta med. Scandinav. **62**:235-254, 1925. (*d*) Von Hagen and Ives.[3] (*e*) Ives, E. R., and Nielsen, J. M.: Disturbance of Body Scheme: Delusion of Absence of Part of Body in Two Cases with Autopsy Verification of the Lesion, Bull. Los Angeles Neurol. Soc. **2**:120-125 (Sept.) 1937. (*f*) Olsen and Ruby.[6] (*g*) Wortis and Dattner.[16] (*h*) Gerstmann, J.: Problem of Imperception of Disease and of Impaired Body Territories with Organic Lesions: Relation to Body Scheme and Its Disorders, Arch. Neurol. & Psychiat. **48**:890-913 (Dec.) 1942. (*i*) Roth.[17]

22. Gerstmann.[21h] Roth.[17]. Spillane, J. D.: Disturbances of the Body Scheme: Anosognosia and Finger Agnosia, Lancet **1**:42-44 (Jan. 10) 1942. Schilder.[2] Bonhoeffer.[11] Holmes, G. H.: Introduction to Clinical Neurology, Baltimore, William Wood & Company, 1946.

23. Von Hagen and Ives.[3] Roth.[17] Raney, A. A., and Nielsen, J. M.: Denial of Blindness (Anton's Syndrome): Two Clinical Cases, Bull. Los Angeles Neurol. Soc. **7**:150-151 (Sept.) 1942.

noted that anosognosia might disappear while the defect remained constant. These facts, and the reproduction of the entire syndrome after intravenous administration of barbiturates would be difficult to explain solely on the basis of a focal lesion and a unitary defect.

In all probability, denial of illness is not uncommonly expressed by patients with brain tumors. Brickner,[24] in a report on lesions of the frontal lobe, referred to "the patient's lack of appreciation of the gravity of the situation." While this has been attributed to lack of judgment, actually the patient's judgment may be very good in areas not concerned with his illness. The syndrome of denial of illness with disorientation and change of affect has also been observed by us in patients after a prefrontal lobotomy for relief of pain.

Anosognosia for impotence or incontinence or denial of illness or operation is not due simply to loss of memory. While disturbance of memory was present, the denial of defect cannot be attributed to it, any more than the anosognosia for hemiplegia can be attributed to the sensory loss which is invariably present in such cases. In case 3 the patient's memory was good for all events except those of the day of operation. In case 7 the patient denied both that the paralyzed limbs belonged to her and that she had been operated on, though she could see her left limbs and feel stimuli applied to them. She was also shown her shaven head and the craniotomy wound in a mirror but still insisted that no operation had been performed.

The pattern of expression for all types of anosognosia showed the same features. Thus, in denying illness or insisting that an operation had not been performed or in ignoring incontinence or hemiplegia, the same kinds of confabulation and the same evasions, euphemisms, displacements and projections were used. It is also significant that in many cases there was anosognosia for more than one defect. The combination of anosognosia for left hemiplegia and blindness has been reported by Weber,[24a] Redlich and Dorsey,[15] Nielsen and Sult,[25] and Roth.[10] Instances are given in which a patient with anosognosia for one defect denied others when they developed. Redlich and Dorsey [15] cited a patient with diabetes, hypertension and retinal hemorrhages who denied his blindness. Shortly after hospitalization he sustained a hemiplegia, which he also denied. Roth [10] reported a case with consecutive anosognosia for blindness, auditory agnosia and left hemiplegia. This suggests that

24. Brickner, R.: The Intellectual Functions of the Frontal Lobes: A Study Based upon Observation of a Man After Partial Bilateral Frontal Lobectomy, New York, The Macmillan Company, 1936.

24a. Weber, F. P.: Agnosia of Hemiplegia and of Blindness After Cerebral Embolism, Lancet **1**:44-46 (Jan. 10) 1942.

25. Nielsen, J. M., and Sult, C. W.: Agnosias and the Body Scheme: Five Clinical Cases, Bull. Los Angeles Neurol. Soc. **4**:69-76 (June) 1939.

there are not multiple lesions which destroy centers in which are represented awareness of various ailments, inadequacies and traumatic experiences but, rather, that there is a reorganization of brain activity in which the patient denies whatever he feels is seriously wrong with him, whether it is a hemiplegia, a craniotomy or a sense of inadequacy. Such a new organization can occur not only with a brain tumor but also after a subarachnoid hemorrhage or after prefrontal lobotomy, when the patient will deny that he has pain or that an operation was performed.

Any explanation of the occurrence of anosognosia in the patients under discussion must consider the fact that it never occurred as an isolated entity but was always an aspect of a more generalized disturbance in behavior. This state was characterized by disorientation, confabulation, amnesias, altered psychomotor activity, language disturbance, "personality" change, illogical thinking and, in some instances, misidentification and hallucination. In some patients the disorientation, language disturbance and change in mood can be easily overlooked and the confabulations not elicited, whereas in others the dysfunction may be so severe as to be labeled "confusion." The alteration in function is best described in the concepts of Hughlings Jackson.[26] Jackson taught that in the damaged brain no single function is lost but that there occurs a process of dissolution in which there is evolved a new pattern of integration that is less complex, more stereotyped and more automatic. Jackson defined consciousness as "the degree of correspondence between the individual and the environment." Our patients appeared to react to only a limited portion of the environment, using certain data and rigidly excluding all else. Thus, the man who each afternoon insisted it was 4 : 00 in the morning used his own sleep habits as his index of time. Another patient stated he was in the firehouse next his home because he could see the chromium-plated poles on the ward and a lot of men in bed who might be firemen. It was also seen in the paraphasic language disturbance in which the patient named objects in terms of only a single aspect of their structure or function.

The person with anosognosia relates to the environment largely in terms of his needs and feelings. His main need is to be well. This, in itself, is not a pathological manifestation but is present in all people. Goldstein [27] called it "the drive to self-actualization." As will be pointed out in a subsequent communication, the character and intensity of this drive are related to the personality pattern. Normally the drive to be

26. Taylor, J.; Holmes, G., and Walshe, F. M. R.: Selected Writings of John Hughlings Jackson: Evolution and Dissolution of the Nervous System, Speech, Various Papers, Addresses and Lectures, London, Hodder & Stoughton, Ltd., 1932, vol. 2.

27. Goldstein, K.: The Organism: A Holistic Approach to Biology Derived from Pathological Data in Man, New York, American Book Company, 1939.

well does not transcend the bounds of reality and does not affect the stability of spatial and temporal orientation. In the milieu of the damaged brain the drive appears in a distorted fashion, that is, as anosognosia. Here the limitations of spatial and temporal orientation no longer operate but are subject to displacements, projections and condensations, often obviously in the direction of denial of illness. The disturbances of spatial orientation in our patients were similar to those described by Paterson and Zangwill [28] in their study of head injuries. The patient may deny that he is in a hospital and say he is home or in a hotel. He may say he is in another hospital, or he may give the correct name of the hospital but locate it nearer his home or even in the same building as his home. In temporal disorientation, he may place himself in a time before the onset of his illness. Even the type of hallucinatory experience may be related, as in the case of the woman who saw her paralyzed limbs lying on the table, "like false teeth."

SUMMARY AND CONCLUSIONS

Anosognosia was observed in 22 cases of brain tumor. The tumors were situated in various parts of the brain, including the frontal, temporal and parietal lobes, the diencephalon and the posterior fossa. In 4 cases the lesions were of metastatic origin. In 17 cases there were increased intracranial pressure and/or subarachnoid bleeding. In the 5 cases without increased intracranial pressure or subarachnoid bleeding the lesions extended across the midline and involved the regions of the third and lateral ventricles. In 16 of the 17 cases with electroencephalographic records, bilaterally diffuse abnormalities were noted.

In all instances the anosognosic delusion involved more than one defect. The aspects of illness which were denied included left hemiplegia, right hemiparesis, involuntary movements of the right lower extremity, blindness, loss of memory, urinary and fecal incontinence, sexual impotence, vomiting and the fact that an operation had been performed or that the patient was ill in any way.

Anosognosia never occurred as a single phenomenon but was manifested as part of a generalized disturbance of behavior. The complete syndrome was manifested by spatial and temporal disorientation, disturbance in psychomotor activity, change in affect and personality organization, alteration in the use of language, mainly of the paraphasic type, and, in some cases, hallucinations.

In 3 of the cases in which anosognosia had disappeared while the defect remained, amobarbital sodium (sodium amytal®) was administered intravenously. This reproduced a pattern of anosognosia, disorientation

28. Paterson, A., and Zangwill, O. L.: Recovery of Spatial Orientation in the Post-Traumatic Confusional State, Brain **67**:54-68 (March) 1944.

and confabulation similar to that which the patient had shown during the period of disturbed behavior.

The phenomenon of anosognosia is not wholly explicable on the basis of a localized defect or as a manifestation of disruption of the "body scheme." It may be better described as the manifestation of the patient's drive to be well, appearing in a new pattern of organization in the damaged brain.

18 West Tenth Street.

Dr. Harry M. Zimmerman, of Montefiore Hospital, furnished the description of the pathological material in case 5.

ONE OPERATION CURES THREE PEOPLE

Effect of Prefrontal Leukotomy on a Case of Folie à Deux et Demie

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THE TERM folie à deux is used to describe the adoption by an otherwise sane person of the delusions of an insane one. The usual setting is that, in circumstances of comparative seclusion, the personality of the sane person is dominated by that of the other. The condition is always of interest for its picturesqueness, as well as for its rarity. The following case is presented on both counts and because it is, so far as I know, the first to be recorded in which prefrontal leukotomy was the method of relief.

REPORT OF CASE

Mrs. F., aged 61, first came under observation in May 1946. All her life she had been a self-conscious, meticulous, overscrupulous, energetic and dominating personality. She was the youngest of eight children, born of stable parents, who had lived until they were over 80. The only evidence of psychiatric abnormality was in one sister, who, at the time of the patient's referral, had for about three years had a mild depressive illness with hypochondriacal features.

The patient had a contented childhood and, on leaving school, worked as a cashier until her marriage, at the age of 21. She had two children. At the time of her coming under observation, these were 40 and 37 years of age, and both were married.

Throughout her successful and happy married life, the patient was always the ruling force, assumed the domestic responsibility and made the decisions as to family welfare, while she always (in his own words) "mothered" her husband. From the beginning she appears to have been house proud, economical without being mean, high principled and rigid. She was especially scrupulous over cleanliness and somewhat morbidly interested in matters of health. She always had to have things straight, could not tolerate things being left undone about the house, was unable to sit in a room with a crooked picture and would not infrequently go downstairs from bed to reassure herself that she had turned out the lights. "If I have a thing in my head," she said, "I have to deal with it," Her daughter remarked, "Once she has got an idea in her head she is very determined and does not let it go."

For much of her married life, Mrs. F. ran a grocery business in a London suburb, in addition to keeping house. This was a profitable venture, and in 1934 she sold it successfully, at the same time that her husband, nine years older than she, and a highly respected and trusted employee of a large organization, retired. They settled down together in the country to enjoy the evening of their days. As

the children had married, they lived alone. Their life was quiet and secluded, with, as its main diversions, gardening, motoring, occasional trips to the cinema and visits to their daughter, who lived 7 or 8 miles away. This idyll continued until September 1945, when the two were going away on a visit together. This was regarded by Mrs. F. as an intrusion in the even tenor of life rather than as a stimulating diversion, and she was irked at having to sit in a crowded and dirty waiting room in a London terminus, among many soldiers. She remarked to her husband that in such a place, and surrounded by such people, they were likely to contract some contagious disease. Mr. F. disagreed, but when, about ten days later, his wife reported that she had found an insect on her pillow he felt that, as usual, she had probably been right.

This discovery led Mrs. F. to much anxiety, expressed in washing, scrubbing and cleaning, which she diligently pursued for some two months. At the end of that time it seemed that, although the further ravages of the insects (which had by now become plural) had been checked, the root cause was still uneradicated. She consulted the sanitary inspector. He stated in a private letter to the hospital that he had seen what he believed to be a garden insect on a blanket shown to him, but that this had escaped before identification was possible. He added that it was "the kind of property where vermin infestation was least likely" and that no traces of such were found on or in another blanket sent for special examination. He felt obliged, however, in view of the anxiety of his clients, to advise fumigation of the bedding. This was carried out, as was fumigation of all Mrs. F.'s personal clothing, while the bedroom was also sprayed with D.D.T. This was successful so far as it caused extermination of all the insects except a few, which, unfortunately, were by then lodged in Mrs. F.'s hair. This led to repeated head washings and, for a short time, to complete depilation, which inhospitality caused migration into the ears as a last place of refuge.

Preoccupation with this matter became extreme and excluded almost all other considerations in life. There were two further consultations with the sanitary inspector and two further fumigations. In order to prevent the menace from spreading, all linen and laundry were washed at home; visits to and from the outside world were reduced to the minimum, and Mr. F. was stood in the bath and was sprayed with D.D.T. three times a week. Meanwhile, arrangements were made to trap the insects inside Mrs. F.'s ears by filter papers impregnated with D.D.T. and by drowning them with instillations of dettol® and olive oil. These maneuvers were successful only in that they kept the insects on the move by driving them out from the ears into the hair, unless the meatus was blocked with cotton wool. The days were spent in devising fresh attacks and the evenings in arranging filter papers and decontaminants as antimacassars.

Local medical consultation having been unhelpful, in that Mrs. F.'s complaint was dismissed as "mere fancy," the patient attended an ear hospital, where she was referred to a neurologist and thence for psychiatric advice.

Meanwhile, the insects had become visible, though they had at first been believed to be ultramicroscopic (since examination of the filter papers and cotton wool pledgets with hand lens, and later through a microscope reluctantly lent by the son-in-law, had proved negative). As time went on, it gradually became accepted that they had been seen and were, indeed, evident to any who cared to look.

During attendance at the hospital, from May 1946 onward, the patient repeatedly brought up pieces of cotton wool in small glass jars; the latter contained minute particles of dust, which were claimed to be entomologic specimens. Mrs. F. several times suggested that the hospital might ask the B.B.C. to broadcast

in the hope that a scientist might be found with knowledge of this special type of insect, which made its habitat only in the ears and back hair. Later the insects were considered to be "definitely foreign," probably of German origin.

The most interesting feature of this case was the effect on the husband and, to a less extent, on the daughter. The former wrote a letter in May 1946 which showed unequivocally that he believed that there was a plague of insects in his house, and which included the statement that he thought it unwise for either himself or his wife to go about in public. At an interview, he said that he did not believe that there were, in fact, any insects in his wife's hair or ears but that he had ceased to argue with her because he felt her conviction to be unshakable. That something of this attitude was a mere concession to medical reasoning, however, was shown, not only by the letter which had antedated the interview, but by his remarks a month after it: "Yes; I think there is something in it—a very minute insect—very small indeed—I have had the opinion 'Oh well, you're right, old lady' and that the insects had disappeared in the wadding. I wonder if she could have something done to disinfect the ear? She wants an X-ray. I am not going to say I believe it simply for her sake, but I do think there's something to it now." And, a month later: "Well, there is evidently something there. I suppose she has been showing you these things. Evidently something. We have taken the trouble to polish out those receptacles, so that they were absolutely clear, but something has got into them. . . . My wife's case is very difficult." His own ears had started to itch a little. "My ear irritates now and again, but I stir it up, and it's all right." But that he was not without doubts about the cause was shown by his answer to the question: "Do you think it is insects?" A. "No, I shouldn't think so." The daughter, an intelligent and attractive person, said frankly that she did not know whether to believe the story or not. After seeing her mother and hearing her talk about it, she thought that it was true. In that she saw her mother about once a month and talked to her on the telephone nearly every morning, she found that for the greater part of the time she believed that there was truth in the insect story; it was only when her husband came home in the evening that she would be temporarily converted to the opposite view. In fact, she could be got to adopt either attitude in conversation, according to the trend of what was said to her, seemingly without awareness of any inconsistency.

It is for this reason that the case has been styled one of "folie à deux et demie," since the husband came fully to participate in the delusion, while the daughter did so only when under the maternal influence.

The patient was admitted to a psychiatric center from October to November 1946, from which she was discharged unimproved, except that she slept a little better. She was admitted to the psychiatric unit of St. George's Hospital in February 1947, where she was noted to be fundamentally depressed, with crying in the mornings and with suicidal preoccupation. This depression had gradually increased since she had first been under observation in the previous year, and it had been accompanied with loss of weight and early waking. She was, by now, entirely preoccupied with her symptoms and was unable to take interest in anything else.

She was treated by electroplexy. After three applications she lost the insects, although the depression itself did not clear until she had had eight treatments. She was discharged as recovered on May 10, 1947; but, in fact, she was not fully well, for she still felt that her symptoms had been caused by insects and she believed that the effect of the treatment had been to electrocute them.

During the ensuing year she was followed in the outpatient department, where she attended regularly. Her circumstances for recovery from what was taken to be a depressive illness were not ideal, as her husband, to whom she was much attached, had been obliged to enter a hospital and to undergo a number of operations. This caused the patient much worry, and on visiting him she was liable to become emotional. Within a month of her discharge from the hospital, the insects had returned to her ears, this time while visiting her daughter, and from then on they continued to trouble her to a variable extent.. At times she would have "only one twinge from the insects" within a month, and at other times they would bother her only at night, while there were certainly periods when she wondered whether her aural symptoms might not be "due to nerves," and not to the insects at all. Within a year of her discharge, however, she had relapsed fully. Her depressive state had become insidiously worse: She again had crying spells and disturbed sleep, was emotional and was tormented by the insects, which she now felt "flicking out" from her ears into her hair, while at other times she would hear them "pinging" into tins containing D.D.T. which she held against her head.

She was readmitted to the psychiatric unit of St. George's Hospital on April 21, 1948, and a prefrontal leukotomy was performed by Mr. Wylie McKissock. From the first postoperative day, she declared that the insects had gone, although, owing to mild postoperative confusion, she did not believe for a few days that the operation had taken place; she also did some knitting with five needles and on a later occasion got lost. She was free from depression and at all times cheerful, though she showed much reduction in spontaneous behavior, with "flattening" of affect. Owing to the latter, she tolerated with insouciance some postoperative urinary incontinence. She did not, however, gain insight into the preoperative delusion. On June 26, 1948, she was discharged from the hospital to a convalescent home, where she remained cheerful and bright, noticeably free from worry, and eating and sleeping well, but with some frequency and urgency of micturition, which led to occasional incontinence, together with inertia and reduction in her spontaneity.

In the 24 months which have elapsed since operation, the patient has steadily improved. She is no longer incontinent; she has never shown any signs of depression, and her tendency to worry has been reduced to an extent which makes her noticeably easier to live with, though this freedom is also attended with some inconvenience, in that she is liable to put off things which she does not want to do, to an extent which renders her standard of living less high than it was. Her manner of life, however, is still satisfactory. She has never been able to explain the disappearance of the insects, nor does she seek to do so; but she has never relinquished her conviction that it was they which were the cause of her trouble, though she never mentions it.

Far more interesting than this result has been the effect on her husband, who remarked: "I tell you one thing we never hear about now, and that's those insects she's supposed to have had. She used to be on about them all the time." Q. "What do you mean, the insects she is supposed to have had? Do you doubt that she had them?" A. "Of course she never had them. It was all nonsense." Nor would he admit that he had ever shared her belief. The daughter, in retrospect, was amused by the affair, and, while commenting that at the time she had never finally decided one way or the other, she at present has no doubts as to the origin of this entomologic plague.

COMMENT

There has never been full agreement as to whether this case was one of involutional depression with hypochondriacal features, which presented in the first place as an obsessional preoccupation, or whether, on the other hand, the condition was paraphrenia. Features of the two conditions were combined. The patient has fully recovered except that she has not gained insight, while she has some postoperative deficits which, in a retired woman, are not of special consequence. The other two affected persons have been fully cured in that neither has any current symptoms, while both have insight. It may therefore be said that the surgeon cured three people by one operation.

SOME BIOCHEMICAL CHANGES OBSERVED DURING AGENE®-INDUCED CONVULSIONS

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THE OBSERVATION was made by Sir Edward Mellanby [1] that dogs maintained on a diet of which the whole wheat portion had been treated with nitrogen trichloride (agene®) exhibited symptoms of "canine hysteria" or "canine epilepsy." This observation initiated a number of studies on the convulsant action of such materials.[2] The experimental production of convulsions by chemical, electrical or surgical means, in the study of epilepsy, has not been altogether satisfactory, in that the convulsive phenomenon usually occurs with such rapidity that investigation of precipitating factors is not really possible.[3] However, nitrogen trichloride intoxication permits one to produce the syndrome of "canine hysteria" over a period of days, during which symptoms cumulate. At a fairly predictable time (dependent on the dose of agenized material) a convulsion occurs, usually followed by several similar seizures; however, the whole syndrome is reversible, provided that excessive doses have not been administered.

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* National Institute of Health Junior Research Fellow, 1946-1949.

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A portion of this work was done by Dr. Bedford in partial fulfilment of the requirements for the degree of Doctor of Philosophy from Yale University.

1. Mellanby, E.: Nutrition Rev. **6**:237, 1948.

2. (*a*) Parry, H.: Lancet **1**:32, 1948. (*b*) Silver, M. L., and Pollock, G. H.: Am. J. Physiol. **154**:439, 1948. (*c*) Erickson, T. C.; Gilson, W. E.; Elvehjem, C. A., and Newell, G. W.: A. Research Nerv. & Ment. Dis., Proc. **26**:164, 1947. (*d*) Silver, M. L.; Zevin, S. S.; Kark, R. M., and Johnson, R. E.: Proc. Soc. Exper. Biol. & Med. **66**:408, 1947. (*e*) Newell, G. W.; Gershoff, S. N.; Fung, F. H., and Elvehjem, C. A.: Am. J. Physiol. **152**:637, 1948. (*f*) Elithorn, A.; Johnson, D. M., and Crosskey, M. A.: Lancet **1**:143, 1949. (*g*) Newell, G. W.; Erickson, T. C.; Gilson, W. E.; Gershoff, S. N., and Elvehjem, C. A.: J. Lab. & Clin. Med. **34**:239, 1949.

3. Penfield, W., and Erickson, T.: Epilepsy and Cerebral Localization: A Study of the Mechanism, Treatment and Prevention of Epileptic Seizures, Springfield, Ill., Charles C Thomas, Publisher, 1941.

The purpose of the present study was to determine whether, in view of the observed similarities between epilepsy induced with nitrogen trichloride and human epilepsy with respect to physical manifestations and electroencephalographic patterns,[2c,d] additional similarities are to be found in the blood chemistry. The possible role of the various chemical entities studied as precipitating factors in the production of a seizure was examined by following these substances through the various stages of the intoxication—the normal, preseizure, seizure and postseizure, or interparoxysmal, stages.

MATERIAL AND METHODS

Mongrel dogs of both sexes, weighing 5 to 12 Kg., were used in the experiments. In the first series of experiments on the determination of serum calcium, magnesium

*Summary of the Results Obtained on Examination of the Various Elements Studied During All Phases of Agene®-Induced Epilepsy in the Dog**

Component Examined	No. of Cases	Values			
		Normal	Preseizure	Seizure	Interparoxysmal
Glucose, Mg./100 cc.					
Arterial	6	86.8	76.2	105.6†	72.8†
Venous	6	69.7	52.8†	106.2†	72.3
A-V	6	17.2	23.3	—0.6	0.5†
Potassium, Mg./100 cc.	6	21.3	22.2	22.9	32.2†
Magnesium, Mg./100 cc.	12	2.12	2.06	2.34	2.50†
Carbon dioxide, volume %					
Arterial	11	37.41	38.70	28.97†	36.60
Venous	11	44.25	44.94	32.19†	41.00†
A-V	11	6.84	6.24	3.22	4.49†
Oxygen, percentage saturation					
Arterial	11	94.3	96.7	93.1	93.9
Venous	11	75.5	75.7	71.1	71.8
A-V	11	18.8	21.0	22.0	22.0
Calcium, mg./100 cc.	8	9.88	9.48	9.64	....
Inorganic phosphorus, mg./100 cc.	6	6.6	7.6	10.1	8.6
Cholinesterase, units	8	1.67	1.64	1.86	....

* The means for each group is calculated, and each value that differs significantly is marked with a dagger.
† Limit of significance, $p = 0.05$.

and cholinesterase, agenized flour (20 Gm. of nitrogen trichloride per hundredweight of flour) was added to a diet described by Silver and associates.[2d]

However, a highly active zein preparation (30 Gm. of nitrogen trichloride per kilogram of flour) became available and was used in all subsequent experiments. Smaller amounts of this toxic material were needed (0.5 Gm. per kilogram per day) and it apparently was not unpalatable, the lack of palatability being the disadvantage of the treated flour (20 Gm. per kilogram per day). In all experiments, the animals received in the control period either whole wheat flour or untreated zein in amounts similar to those used in the experimental period.

Before any study was commenced, several control samples of blood (venous from the internal jugular vein, arterial from the femoral artery) were obtained with the animals first on standard laboratory chow, and then on a diet to which the unagenized agent (whole wheat flour or zein had been added). After this, the animals were fed the agene-treated materials, and samples of blood were taken at intervals throughout the course of the intoxication.

Blood concentrations of the following constituents were determined: calcium, magnesium, potassium, inorganic phosphorus, glucose, carbon dioxide, oxygen and cholinesterase. The methods used were as follows: calcium, the Clark-Collip modification of the Kramer-Tisdall method [4]; magnesium, Denis' method [4]; potassium, Cuming's micromethod [5]; inorganic phosphorus, the Lowry-Lopez method [6]; glucose, Somogyi's method [7]; gases, the Van Slyke method [4] and cholinesterase, the Hall-Lucas method.[8]

The results are presented in the form of graphs, while a summary of the determined values are presented in the accompanying table. The values which differ significantly from normal are marked with daggers.

OBSERVATIONS

Blood Glucose.—Chart 1 presents a graphic analysis of glucose values in arterial and venous blood. It will be seen that there is a significant fall in venous glucose in the preseizure stage, as compared with the normal, while values for arterial glucose at this stage are approaching significance in a downward trend. The arteriovenous differences are not significant at this stage. During the fit there is a significant increase in both arterial and venous glucose as compared with the normal, and the arteriovenous differences are suggestive of a narrowing. On comparison of values for the normal and for the interparoxysmal stage, it is seen that there is a significant drop in glucose in the arterial blood and that the arteriovenous differences have significantly narrowed.

Comment: A number of investigators have reported that in human epilepsy the blood sugar is normal in the interparoxysmal period.[9] Others have stated that in the period preceding the fit there was a tendency to hypoglycemia, which changed to hyperglycemia at the time of the seizure. On the other hand, Barlocco [9a] found blood glucose values above normal before a seizure and normal at the time of the fit.

Hewetson [10] in 27 samples of blood, taken from dogs subject to spontaneous "canine hysteria," observed a range of venous glucose of 80 to 148 mg. per 100 cc. He interpreted these values as essentially normal and the values at the upper limit as being the result of excitement.

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4. Hawk, P. B.; Oser, B. L., and Summerson, W. H.: Practical Physiological Chemistry, ed. 12, Philadelphia, The Blakiston Company, 1947.

5. Cumings, J. N.: J. Clin. Path. **1**:173, 1948.

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9. (*a*) Goldstein, H., and McFarland, R. A.: Am. J. Psychiat. **96**:771, 1940. (*b*) Lennox, W. G., and Cobb, S.: Medicine **7**:105, 1928.

10. Hewetson, H. R.: Hysteria in Dogs, read before the Fifty-Fourth Annual Congress of the National Veterinary Medical Association of Great Britain and Ireland, Sept. 14-18, 1936.

In a report on "canine hysteria" produced by a diet of agenized wheat gluten, Newell and associates [2e] presented venous glucose values for three dogs, which they stated were representative of a larger number of animals. The determinations were made several days after the onset of fits, and an occasional reading during a fit was included with the interparoxysmal values. The authors concluded that there were no consistent or significant differences in blood glucose values, even at the time of the fit.

It is evident, then, that the present findings are not in agreement with other investigations of "canine epilepsy," but do tend to confirm the results of those studies on human epilepsy which show a fall in blood glucose prior to the convulsion and a rise at the time of the seizure.

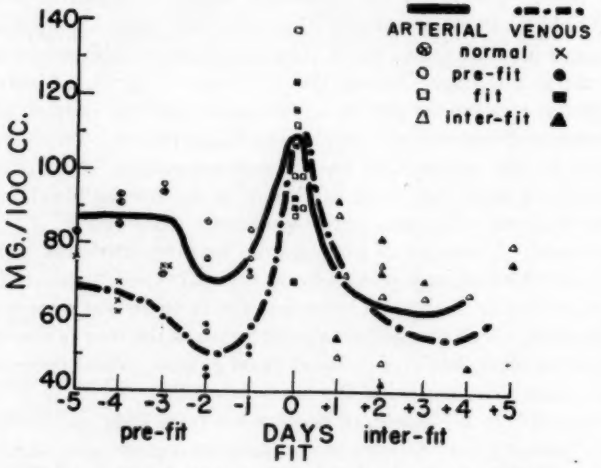

Chart 1.—Trend of blood glucose in stages of canine epilepsy.

Whereas, in agreement with reports there was no change in venous glucose in the interparoxysmal period, a fall in arterial glucose was observed at this stage. Since most reports on human epilepsy have considered only values for venous blood, no reports on arterial glucose are available for comparison.

While a significant decrease in glucose values was observed prior to a fit, it is questionable what significance this decrease might have in the production of the convulsion, since there are many instances of lowered blood sugar levels without any convulsive tendency. Blood sugar values as low as 25 mg. per 100 cc. have been reported [9b] in human subjects without concomitant convulsions. The narrowing of the arteriovenous differences during the abnormal phases, with significantly low values in the interparoxysmal stage, is of interest. This narrowing may

be a contribution of the extrahepatic tissues to the homeostasis of the glycemic level during hypoglycemic states, resulting from the sharp drop in the rate of glucose assimilation of the extrahepatic tissues at the onset of hypoglycemia, thus retarding the depletion of blood sugar.[11]

Serum Potassium.—In chart 2 is presented a graphic analysis of serum potassium values. While no significant changes appear prior to the fit or at the time of the first fit on comparison with the normal values, there is, however, a significant increase of potassium in the interparoxysmal stage.

Comment: It is well recognized that an increase or a decrease of potassium in the fluid perfusing a neuromuscular preparation produces

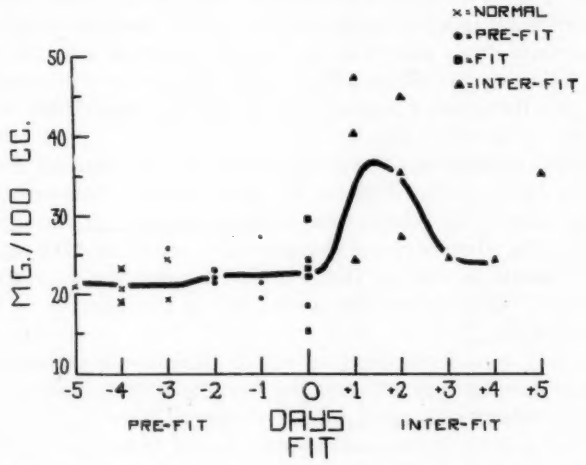

Chart 2.—Trend of serum potassium in stages of canine epilepsy.

profound modifications in the excitability of nerve and muscle.[7] The excitatory action of the potassium ion can further be demonstrated at the level of the ganglionic synapse.[12] The central nervous system is equally sensitive to variations in the concentration of this ion.[13]

There is a fund of excitation phenomena whose common characteristic is the loss of the potassium ion, and the presence of bioelectric currents is almost certainly bound up with these ionic changes. The importance of the potassium ion has been amply elaborated in many theories, all tending to show that excitation modifies the permeability

11. Somogyi, M.: J. Biol. Chem. **174**:597; 189, 1948.

12. Feldberg, W., and Vertianen, A.: J. Physiol. **83**:103, 1934.

13. Zwemer, R. L., and Cicardo, V. H.: Rev. Soc. argent. de biol. **17**:254, 1941.

of membranes, so that the potassium ion is enabled to migrate to the exterior, with momentary depolarization of the membrane in question and the propagation of the impulse.[14]

According to Zagami,[15] experimental epilepsy in the dog produced by electrical stimulation of the cerebral cortex is accompanied with an increase of plasma potassium, but the origin of this increase in potassium, which may have come from muscular contractions, was not made clear.

McQuarrie was able to show an increase in serum potassium during convulsions in human epilepsy. It was reported that this increase antedated the convulsions by 36 hours, and it was thus postulated that there occurs a "leakage of potassium from cells," accompanied with increased permeability of the surface of the nerve cells, which acts as the etiologic factor in the epileptic convulsion.[3] Recently, Cicardo [16] has shown in experimental epilepsy induced in the dog by electrical stimulation or by convulsant drugs that there is a loss of potassium from the cerebral tissues following stimulation. These same changes were observed in the blood from the superior sagittal sinus in animals immobilized by curare or section of the spinal cord.[14]

Newell and associates [2e] reported an increase of potassium in the days following the appearance of fits in agene®-induced "canine hysteria." Corroboration of this observation is presented here; at the same time, it is noted that there were no changes up to and at the time of the first fit. This seems to indicate that the rise in potassium is a secondary phenomenon and does not play a vital role in the initiation of the first seizure.

However, considering the vital role of potassium in nervous activity, one might speculate that, although the loss of potassium from the cell into the extracellular fluid is not a primary etiological factor in the production of the first seizure, it may possibly play a part in the predisposition to successive seizures.

Serum Magnesium.—In chart 3 a graphic analysis of serum magnesium values is presented. A significant rise in magnesium is noted in the interparoxysmal stage as compared with the normal, while no other significant changes were noted.

Comment: Magnesium, like calcium, is an ion of considerable physiological importance and apparently is essential to the integrity of the neuromuscular system.[17] Pharmacologically, in high concentrations it is

14. Cicardo, V. H.: J. Nerv. & Ment. Dis. **101**:527, 1945.

15. Zagami, V.: Arch. di sc. biol. **11**:301, 1928.

16. Cicardo, V. H.; Torino, A., and Fendrick, B.: Rev. Soc. argent. de biol. **18**:308, 1942.

17. Goodman, L., and Gilman, A.: The Pharmacological Basis of Therapeutics: A Textbook of Pharmacology, Toxicology and Therapeutics for Physicians and Medical Students, New York, The Macmillan Company, 1941.

a depressant of the central nervous system. It has excited the interest of several investigators, who thought that it might be a factor in the causation of epilepsy.

Greenberg and Aird [18] determined the blood magnesium in 28 epileptics; although an abnormal degree of variability was observed, the mathematical mean approached normal values. Hirschfelder and Haury [3] observed that, whereas plasma magnesium was normal in epileptics not undergoing seizures, there was a low magnesium level during or just prior to an attack. Hewetson,[10] in his study of "canine hysteria," reported essentially normal magnesium levels in the interparoxysmal state, although the range of 1.5 to 2.6 mg. per 100 cc. was considered wider than usual. Newell and associates,[2e] in their investigations of

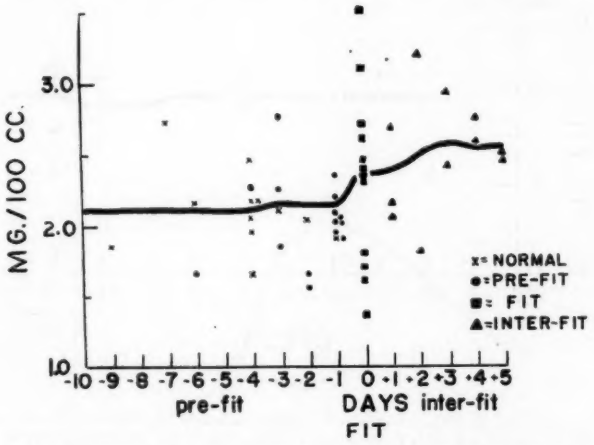

Chart 3.—Trend of serum magnesium in stages of canine epilepsy.

agene®-induced "canine hysteria," observed an interparoxysmal rise in serum magnesium. This is confirmed in the present results, and it was observed that there was no change in serum magnesium in the days preceding the first fit or during the phases of the fit during which determinations were made.

At the moment, these findings of increased serum magnesium and potassium level in the interparoxysmal state appear difficult to reconcile with the reported inverse relation of potassium and magnesium found in human epilepsy,[3] as well as with the magnesium-potassium antagonism noted by Smith.[19]

18. Greenberg, D. M., and Aird, R. B.: Proc. Soc. Exper. Biol. & Med. **37**:618, 1938.

19. Smith, S. G.: Arch. Biochem. **20**:473, 1949.

Serum Calcium.—A graphic analysis of serum calcium values is presented in chart 4. It will be seen that no significant changes occurred in serum calcium during any of the phases of the seizure in which examinations were made.

Comment: Lennox and Cobb [9b] stated that, "though calcium constitutes only 3 per cent of the total base of the blood serum, its possible variation in epilepsy has interested many workers. This is because of the well known relationship between increased irritability of nerves and decreased blood concentration in tetany and the relation of calcium to the permeability of capillaries," which later may be related to the precipitation of seizures.

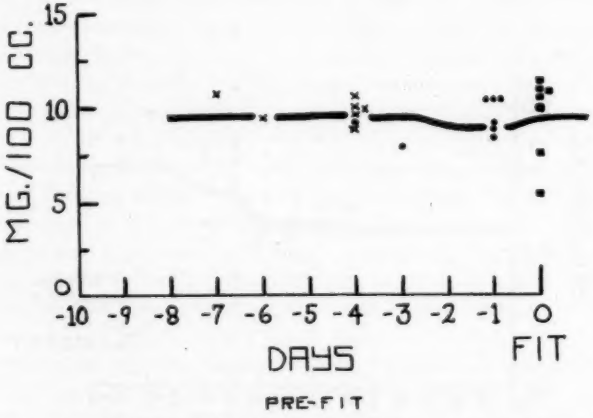

Chart 4.—Trend of serum calcium in stages of canine epilepsy. Crosses indicate normal values; black circles, preseizure values, and black squares, seizure values.

In cases of human epilepsy, the results of calcium studies have shown a general lack of agreement. Some investigators have reported normal calcium values for the epileptic patient, and there is general agreement that the serum calcium is normal in the interval between attacks.[9] Other investigators, however, have failed to confirm these results, some reporting an increase and others a decrease in calcium.[9a]

Hewetson [10] reported essentially normal serum calcium values, with a range of 8.0 to 11.2 mg. per 100 cc., in spontaneous "canine hysteria." He believed that further work would be necessary before any definite conclusions could be made regarding the possible role of calcium.

Newell [2e] reported normal serum calcium in the interparoxysmal and occasional seizure stages of agene®-induced "canine epilepsy"; and, on the basis of the present studies, it is possible to state that there is no change in serum calcium prior to the first fit or during the fit.

Serum Inorganic Phosphorus.—Chart 5 presents a graphic analysis of the values for serum inorganic phosphorus. Although there is no absolute difference of statistical significance in phosphorus values in any of the stages, it will be seen that on the day preceding the fit there is an upward trend, and that during the fit the values approach statistical significance ($p = 5$ to 10 per cent).

Comment: In the literature there are reports indicating that in human epilepsy the levels of serum inorganic phosphorus are normal. Mondio [9a] noted normal values in epileptics but also observed that epileptic patients with few attacks had lower levels than did those with more frequent attacks. Other investigators have reported increased

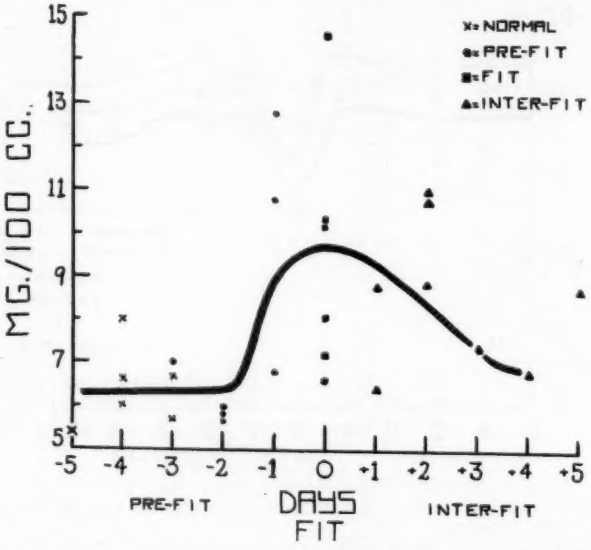

Chart 5.—Trend of serum inorganic phosphorus in stages of canine epilepsy.

phosphorus levels in the preconvulsive phase, the convulsive phase and the interparoxysmal period.

Weil and Liebert [9a] and Coombs and associates [20] observed an increase in serum phosphorus in experimental epilepsy and suggested that, since the increase was absent in the curarized animal, the increase in phosphorus must arise from the musculature. Recently Cicardo,[21] in experiments with animals immobilized by spinal section, has obtained evidence that during cerebral stimulation by chemical or electrical means there is a liberation of phosphorus from cerebral tissues.

20. Coombs, H. C.; Searle, D. S., and Pike, F. H.: Am. J. Psychiat. **13**:761, 1934.

21. Cicardo, V. H.: Am. J. Physiol. **145**:542, 1945.

Newell [2e] reported normal phosphorus values in the days following agene®-induced convulsions. The present findings tend to support this finding in the interparoxysmal phase; however, the increases in the serum phosphorus noted in the preseizure and seizure phases, while of limited significance, suggest that changes in phosphorus may be of a primary nature.

Blood Gases.—Charts 6 and 7 present graphic analyses of the oxygen saturation and carbon dioxide content of arterial and venous blood. No significant changes in oxygen saturation are observed. However, there are a significant fall of carbon dioxide content in both arterial and venous blood and a suggestive narrowing of the arteriovenous differences at the

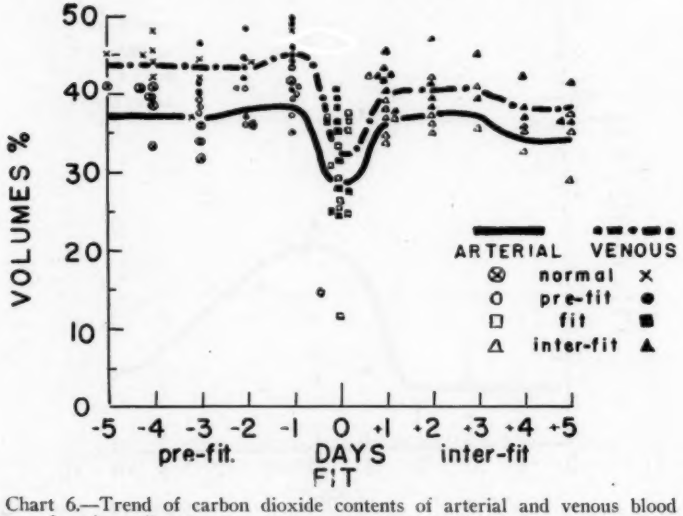

Chart 6.—Trend of carbon dioxide contents of arterial and venous blood in stages of canine epilepsy.

time of the fit. There is also a significant decrease in carbon dioxide in venous blood in the interparoxysmal phase, as well as a significant narrowing of the arteriovenous difference in that stage, as compared with the normal.

Comment: Several investigators have observed essentially normal values for blood gases in the epileptic patient. Normal oxygen and carbon dioxide levels have been noted in arterial blood, as well as in the blood from the internal jugular and antecubital veins.[9a] More recently, Gibbs, Lennox and Gibbs [22] determined the carbon dioxide content of the blood

22. Gibbs, E. L.; Lennox, W. G., and Gibbs, F. A.: Variations in Carbon Dioxide Content of Blood in Epilepsy, Arch. Neurol. & Psychiat. **43**:223 (Feb.) 1940.

in epileptic patients and noted that the carbon dioxide values for both arterial and internal jugular venous blood tended to be abnormally low in patients with petit mal and abnormally high in patients with grand mal. However, it was acknowledged that other factors besides carbon dioxide content must be involved, because seizures are not precipitated in normal subjects by similar deviations in carbon dioxide content and because, even in epileptic patients, more extreme artificial alterations in carbon dioxide must be produced to induce seizures.

Lennox and Gibbs [9a] made 100 measurements on blood taken from the antecubital vein of epileptic patients and found a mild degree of anoxemia to exist. However, this was attributed to a sluggish peripheral circulation, accompanying poor physique, posture, etc., and was not

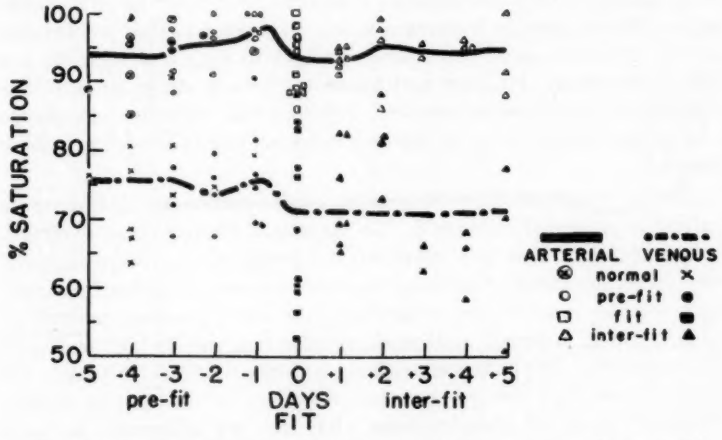

Chart 7.—Trend of oxygen saturation of arterial and venous blood in stages of canine epilepsy.

considered necessarily symptomatic of epilepsy. In another study, Lennox and Gibbs [9a] measured the oxygen saturation of arterial blood (femoral, radial or brachial artery) 125 times in 88 epileptic subjects. They found that the average saturation was 93.4 per cent, which was slightly below that for normal persons (94 to 99 per cent) as reported in the literature. Fifty-four per cent of the patients had oxygen saturations within the normal range. It is of interest that in a study of 58 nonepileptic patients with neurological diseases it was found that only 46 per cent had normal oxygen saturation values. Thus, the degree of oxygen desaturation which the majority of the epileptic patients exhibited was not in itself sufficient to explain the seizures, although it may have been a contributing factor.

The present observations on blood gases are essentially in agreement with the findings in cases of human epilepsy. As in human epilepsy, there were no significant changes in the oxygen saturation of arterial and venous blood, an observation tending to confirm the suggestion of Lennox and Gibbs that low oxygen saturation is not symptomatic of epilepsy and is not in itself sufficient to explain the seizures.

The values for carbon dioxide in our experiments show a significant decrease in the arterial and venous blood during the fit, and this in part may be due to the hyperventilation exhibited by the animal at this time. A decrease in carbon dioxide was noted in the venous blood in the interparoxysmal state. These facts are not necessarily in conflict with the results of studies on human epilepsy, in which Gibbs and associates [22] found that high values for carbon dioxide occurred frequently in cases of grand mal. These investigators contended that other factors besides carbon dioxide must be implicated in seizures, since, as they pointed out, normal subjects exposed to similar changes in carbon dioxide do not have convulsions. Hendley and associates,[23] in a study on acid-base balance and experimental seizures, reported that sensitivity to change in acid-base balance is by no means a universal occurrence in convulsive disorders.

Serum Cholinesterase.—A graphic representation of cholinesterase activity is presented in chart 8. No significant changes were observed. It is unfortunate that this study did not consider the interparoxysmal stage in greater detail. Additional experiments were carried out to determine whether a synergism existed between the convulsant activity of agene®-treated materials and such convulsive agents as metrazol® and physostigmine. Pretreatment with agene®-treated flour (10 Gm. per kilogram per day) for ten days had no effect on the activity of subconvulsant doses of physostigmine (100 mg. per kilogram) of body weight, whereas administration of subconvulsant doses of metrazol® (10 mg. per kilogram) resulted in convulsions in six of nine animals.

Comment: The finding of unaltered cholinesterase activity of the serum in cases of "canine epilepsy" is in agreement with the report of Schutz,[24] who noted that patients with mild epilepsy, and under no treatment for at least three weeks, displayed no change in serum cholinesterase activity. Other investigators,[25] however, have reported low values in epileptic patients, but it is not clear whether these patients were under medication. It has been shown [26] that such acute conditions

23. Hendley, C. D.; Davenport, H. W., and Toman, J. E. P.: Am. J. Physiol. **153**:580, 1948.

24. Schutz, F.: Quart. J. Exper. Physiol. **33**:35, 1944.

25. Stedman, E., and Russell, W. R.: Biochem. J. **31**:1987, 1937. Tod, H., and Jones, H. S.: Quart. J. Med. **6**:1, 1937.

26. Schutz, F.: J. Physiol. **102**:259, 1943.

as anaphylactic shock, metrazol® convulsions and severe muscular activity do not alter cholinesterase activity to an appreciable degree. In addition, studies using unanesthetized rabbits have shown that prolonged anoxia, hypoglycemia or convulsions do not alter the cholinesterase activity of the hemispheres and brain stem.[27]

In view of these facts, it is difficult to believe that cholinesterase per se has a significant role in the development of convulsions. In the reported studies, the dose of physostigmine (100 mg. per kilogram) supposedly lowers the serum cholinesterase by 95 per cent, and yet the dogs "sensitized" with the subconvulsant ration of agenized flour did not have convulsions when this dose was administered. Radomski and

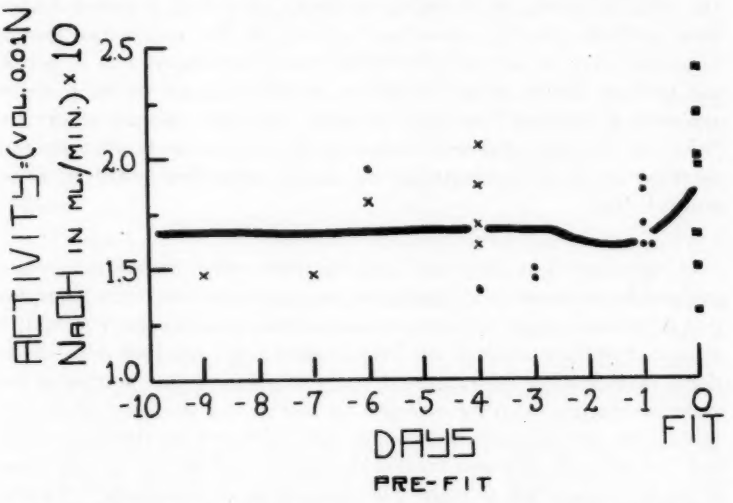

Chart 8.—Trend of serum choline esterase activity in stages of canine epilepsy. Crosses indicate normal values; black circles, preseizure values, and black squares, seizure values.

Woodard [27] reported a similar lack of effect of physostigmine. Further, Cortell and associates [28] have shown that the cholinesterase content of the hemispheres and brain stem may be inhibited in vivo by 50 per cent or more, with consequent increase of the acetylcholine content of the central nervous system, without grossly disturbing its functions. These facts do not exclude the possibility that other enzymes are involved in the convulsive phenomenon.[24]

27. Radomski, J. L., and Woodard, G.: J. Pharmacol. & Exper. Therap. **95**:429, 1949.

28. Cortell, R.; Feldman, J., and Gellhorn, E.: Am. J. Physiol. **132**:588, 1941.

Convulsions might be due to an increased synthesis of acetylcholine. Torda and Wolff [29] have shown that many of the convulsion-producing agents cause an accumulation or sudden increase of acetylcholine by increasing acetylcholine synthesis (e. g., metrazol®; picrotoxin). While it cannot definitely be stated that this is also the case with the agenized flour diet, the fact that subconvulsant doses of metrazol® seemed to "trigger" a seizure in agene®-"sensitized" dogs (also noted by Radomski and Woodard [27]) permits the possible conjecture that under a subconvulsant agene® diet there is a gradual accumulation of acetylcholine, which then requires only a "push" over the critical point by a subconvulsant dose of metrazol,® which in itself is ineffective.

While acetylcholine may precipitate convulsions or may augment the effect of convulsion-inducing agents or processes, it is not evident from available data that disturbance of acetylcholine metabolism leading to accumulation of acetylcholine in the central nervous system is, per se, the primary factor in the induction of fits.[29] However, in a recent report [30] it is noted that dogs severely poisoned with agene®-treated flour, and having exhibited convulsions for a number of days, show a decrease in serum cholinesterase and, at the same time, a rise in serum acetylcholine.

GENERAL CONSIDERATIONS

Originally it was suggested [1] that the treatment of flour with nitrogen trichloride produced an alteration in the protein portion of the flour and that the toxicity might well be due to a toxic polypeptide. More recently [31] a toxic crystalline material has been isolated from agenized zein. Additional investigation has suggested that methionine is the portion of the molecule reacting with the nitrogen trichloride, for proteins deficient in methionine, or in which methionine was destroyed by chemical action and treated with nitrogen trichloride, do not exhibit the typical signs of toxicity when fed to dogs. The observation of Heathcote [32] that the toxicity of the crystalline toxic factor on Leuconostoc mesenteroides P 60 could be reversed by addition of excess methionine also tends to implicate methionine.

While experiments involving human subjects have led to the conclusion that agenized material is unlikely to produce convulsions, it is clear from the discussion of the various entities examined in this report that in the condition of induced "canine epilepsy" there are a number of biochemical changes in the blood which are similar to those reported in human epilepsy.

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29. Torda, C., and Wolff, H. G.: Am. J. Physiol. **151**:345, 1947.

30. Monahan, E. P., and Lalanne, C. G.: Am. J. Physiol. **159**:298, 1949.

31. Bentley, H. R., and others: Nature, London **164**:438, 1949; ibid. **165**:150, 1950.

32. Heathcote, J. G.: Lancet **1**:1130, 1949.

However, the only significant change which might be considered to be primary was the decrease in glucose in the venous blood prior to the initial convulsion. This decrease was certainly not to levels that were in themselves necessarily productive of convulsive attacks, and one is at some loss to assess the importance of such a finding.

A number of other findings of significance were observed at the time of the first fit and between paroxysms of convulsions, but it is probably proper to regard these as secondary manifestations of the initial convulsion and the series of events that are established with it.

On the basis of the findings reported in this study, and those of other investigators, it would appear that the state of induced canine "epilepsy" would be a profitable field for further investigation, in an attempt to elucidate factors involved in convulsive disorders.

SUMMARY

It is shown that there are biochemical changes in the blood of dogs exhibiting canine "epilepsy" induced by agene®-treated proteins that are similar to those reported to occur in human epilepsy.

The observed changes, which are described in detail, are briefly as follows:

1. Glucose: (*a*) A significant decrease in venous glucose prior to the first convulsive attack.
   (*b*) A significant rise in both arterial and venous glucose during the convulsion. The arterial glucose is lower than normal in the interparoxysmal stage.
2. Serum potassium and magnesium: A rise in the interparoxysmal stage.
3. Carbon dioxide: A decrease in both the arterial and the venous blood during the convulsive attack, with persisting levels below normal in the venous blood in the interparoxysmal period.
4. Calcium, oxygen and cholinesterase: No changes at any stage.
5. Serum inorganic phosphorus: Whereas the serum inorganic phosphorus was not found to change significantly, there was a suggestive rise at the time of the convulsive attack.

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CÉCILE AND OSKAR VOGT

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IN ONE of his letters from Germany, describing the atmosphere of scientific life in that country, William Osler wrote in 1890: "I should say that the characteristic which stands out in bold relief in German scientific life is the paramount importance of knowledge for its own sake. To know certain things thoroughly and to contribute to an increase in our knowledge of them seems to satisfy the ambition of many of the best minds." No more suitable words of introduction could be found for this address, which is devoted to the jubilee of Cécile and Oskar Vogt, for these two scholars most aptly personify those values of scientific vocation. They have devoted their lives entirely to "knowledge for its own sake"; the thoroughness of their observation is above criticism, and nothing can satisfy their ambitions more fully, or make their happiness more complete, than a new contribution to "our knowledge of things."

This year Cécile and Oskar Vogt are celebrating a rather remarkable anniversary—she her seventy-fifth and he his eightieth birthday; both enjoying good health, with plenty of energy; both working without interruption on problems which have occupied their minds for more than half a century!

Cécile Mugnier was born in France, in the province of Haute-Savoie on March 27, 1875. She graduated from the Medical Faculty in Paris in 1900, where she was working under Pierre Marie. In 1898, she met in Paris a young German doctor, Oskar Vogt, who had come to study in the famous Paris school of neurology.

Oskar Vogt was born in northern Germany on April 6, 1870. He graduated from the Medical Faculty of Jena University in 1893, after two years as assistant in its department of anatomy. The next three years were spent with Binswanger (Jena), August Forel and others. In 1896 he went to Paris. There he met his future wife. They were married in 1899.

From the Department of Neurology and Neurosurgery, McGill University, and the Montreal Neurological Institute.

Read before the Montreal Neurological Society on March 8, 1950, at the special meeting in celebration of the seventy-fifth and the eightieth birthday of Cécile and Oskar Vogt.

The Vogts made their home in Berlin. The prospect of an academic career never attracted them. They went their own way, their goal being to create a special institute for the study of the brain. As early as the nineties of the last century they understood that brain research must be carried on by a variety of methods; they rightly anticipated that the multitude of problems to be encountered requires a team of workers, specialized in different branches of biology and medicine. They wanted to create a central institution, which would include a kind of brain reference library, in which normal and pathological brains, cut serially throughout their entire length, would be available for study for their own, as well as for coming generations. On May 15, 1898, Oskar Vogt was able to open in Berlin the "Neurologisches Zentral Institut," which four years later acquired the name of "Neurobiologisches Institut," and in 1916 that of "Kaiser Wilhelm Institut für Hirnforschung." But not until 1931 did their Institute obtain adequate accommodation, when funds, provided by the Rockefeller Foundation, permitted building a Brain Research Institute according to the Vogts' own plans, in Buch, a suburb of Berlin. The Institute comprised the following departments: anatomy, physiology, psychology, phonetics, genetics, chemistry, photography and electronics, as well as a clinical ward for 60 patients.

In 1937, Oskar Vogt was forced by the Nazis to resign from the post of director of the Institute. Then the Vogts moved to a small village in the Black Forest—Neustadt—where, with their own funds, assisted by a grant from the Krupp family, they built a small institute, in which they still work.

It must be added that in the third decade of this century they spent considerable time in Moscow, where, after the death of Lenin, the Bolshevist government entrusted to the Vogts the task of creating a Brain Research Institute, in which the brain of their leader might be scientifically investigated.

Turning now to scientific problems, it is interesting to note a fact little known—that the Vogts, though always interested in morphology, were in the earliest years of their work predominantly concerned with psychological questions. I shall let Oskar Vogt himself tell how they happened to change from psychological to morphological studies. In one of his letters he says:

> In order to understand my scientific efforts and their development, it must be realized that since boyhood I have been interested in two fields of knowledge, the mind-body problem and the problem of evolution. At the time of my medical course the study of evolution was of a rather speculative character, whereas the mind-body problem seemed to be more readily approachable by empirical methods. So I decided to devote my time chiefly to the latter problem, without, however, neglecting entirely the problem of evolution. The cultivation of both branches of science led me later to some rather important correlations.[1]

1. All quotations from the writings of C. and O. Vogt which are used in this paper have been translated from the German by the author.

However, the psychological approach to the mind-body problem brought the Vogts no complete satisfaction. First, the results seemed to them too indefinite; second, they became disappointed, owing to the fact that they were unable to bring permanent relief to their neurological patients. This was impossible not only in organic but also in the so-called functional diseases. Oskar Vogt states:

> I have always found that a predisposition is the ultimate basis of the patient's disease. A somatic background is present, which either produces abnormal psychological reactions, i. e., psychopathies, or leads to progressive somatic changes, which cause psychoses. Only the discovery of this somatic background can make successful therapy and prophylaxis possible. We have hoped to gain these insights from a sufficiently intensive study of brain pathology.

And so the final program of their work became definitely established: The ultimate aim was a better understanding of the "phenomena of consciousness and the correlation of these phenomena with the material processes in the brain." To accomplish that, the study of localization seemed to be the best approach; this study had to be based on a thorough knowledge of normal anatomy as a foundation for all further deductions; on this basis, the function of different morphological units had to be studied by the application of experiments on animals and the use of human pathological material.

The first task was to find an anatomic method suitable for the problem of localization. Though this question seems simple today, it was not so 50 years ago. The first anatomic papers by the Vogts dealt with the problem of myelogenesis. They confirmed Flechsig's observation regarding the nonsimultaneous myelination of different parts of the brain, and they found a general homology in the sequence of myelination in different mammals. The Vogts also found that myelination progresses gradually in space and time, and that the areas of simultaneous myelination show different structures, connections and functions. These findings, together with some other, less important ones, showed the Vogts that Flechsig's myelogenetic subdivision of the cortex cannot form a basis for the study of localization. So they discontinued using this method and turned to architectonics, which finally became their most important morphological method in the study of brain anatomy.

By the term architectonics the Vogts mean the study of local differences in the arrangement, the number and the structure of specific elements of the central nervous system. Depending on the method of staining applied, a cyto-, myelo-, fibrillo-, glio- or angioarchitectonics can be distinguished, the first two being the most important. While the myeloarchitectonic differences are more evident and can often be seen even macroscopically, cytoarchitectonic differences are finer and more delicate and so enable more precise localization. The morphological units

distinguished by myeloarchitectonics or cytoarchitectonics are called nuclei in subcortical regions and are defined as areas in the cortex. Subdivision of the cortex led the Vogts and their co-workers to distinguish finally some 200 areas, the myeloarchitectonic corresponding closely to the cytoarchitectonic, each method substantiating the correctness of the other. In the subcortical regions the Vogts' attention was first concentrated on the thalamus and the basal ganglia. In 1909 Cécile Vogt published a myeloarchitectonic atlas of the thalamus of the monkey. At the time, using human developmental material, as well as the results of Marchi degeneration in monkeys, she found that different thalamic nuclei receive different systems of fibers. The study of the basal ganglia led the Vogts to combine the nucleus caudatus and the putamen under the name of striatum and to set this structure in contrast to the pallidum —a conception which is now generally adopted. Besides, their knowledge of the normal anatomy of those structures has formed the basis for their further pathological studies.

Architectonics is not a popular branch of neuroanatomy: It is time consuming; it is not spectacular; it requires a costly laboratory technic and expensive publications; it demands an investigator with a good visual memory. In spite of all this and certain other adverse criticism, it is used, and it will continue to be used, by everyone interested in problems of localization, for, in order to localize a function or a termination of a given pathway, one needs a landmark, and this landmark can be provided by architectonics only. In addition, there exists a completely uncharted field of individual and racial anatomy of the brain, in the study of which architectonics will be the method of choice. But it would be a bad service rendered to architectonics to think of it as a panacea for all the problems of neurobiology. Never have the Vogts underestimated the value of other methods; they have always warned against a generalization of results gained by architectonics alone. In 1926, at the meeting of the German Association for Psychiatry, in discussion with von Economo, Oskar Vogt said:

> To define the koniocortex as sensitive and to call the neighboring areas parasensitive, and even to attribute a definite function to some special nerve cell, is something which architectonics has no right whatsoever to do. These deductions can be made on the basis of physiological methods only.

This brings us to the second method applied by the Vogts on their path to the final goal—that of physiological experiment on animals. From 1903 to 1918, that is, over a period of 15 years, physiological experiment was routine work in their Institute. The results of those experiments were published in two papers; in 1907, in "Zur Kenntnis der elektrisch erregbaren Hirnrindengebiete bei den Säugetieren," and, in 1919, in "Allgemeine Ergebnisse unserer Hirnforschung." The results

of stimulation, using the weakest possible current, formed the content of the first paper. Eighty-three animals, ranging from orang-utan to marsupials, were investigated. The Vogts found in all animals a well delineated "main excitable area"—we call it today the motor cortex—showing in all species the same principle of somatotopic arrangement. The development of individual subareas related to special parts of the body was found unequal in different animals; this was correlated by the Vogts with the unequal functional differentiation of the part of the body under consideration. For instance, the tail area in the kangaroo was found to be extremely small, whereas in the Ateles it was very large and easily excitable. The kangaroo uses its tail to help in jumping—perhaps an important, but rather crude, movement; the Ateles, on the contrary, are able to perform with the tail the finest and most skilful movements. It was found, in general, that in the primates the limb area is better developed, whereas in the lower mammals the head area is better developed; this corresponds with our daily observation of the role which limbs and head play in the lives of different animals, as well as in our own. Besides the "main excitable area," two other areas were described: the eye area, which was found in all animals but the hedgehog, and the temporal excitable area, which was especially large and easily excitable in the bat. This last observation led the Vogts to make an assumption that the bat, which, as was already known, can perceive distant objects without vision, receives corresponding sensations through the ear.

In the second paper, the Vogts described the results of cortical stimulation in 150 monkeys. This time they used a stronger current, applied isolation or undercutting procedures and occasionally stimulated two points simultaneously. On the basis of these experiments, they distinguished 16 areas, which correspond closely to the architectonic subdivision of the cortex investigated. After the stimulation, they used to make an incision at the physiological border of the area and investigate the sections microscopically, thus correlating the results of physiological and anatomic methods. The undercutting and isolation of the stimulated cortex were performed in order to obtain more information about the pathway of the stimulus. To cite only one example, the stimulation of the area 6 a α gave, as a first effect, isolated movements and, as a second, complex movements. The isolation of this area from area 4 abolished isolated movements, whereas the undercutting of the area 6 a α stopped complex movements. The logical explanation was that the pathway for isolated movements runs via area 4, whereas the complex movements are effected by a direct centripetal pathway. The simultaneous stimulation of two different points led the Vogts to the discovery of the suppression phenomenon, as we call it today. They observed that the movements induced by the stimulation of area 4 ceased if area 8 was

stimulated at the same time. The clearest suppression was observed in mastication, whereas the effect on the movements of the face and arm was rather indefinite.

Since 1918, the Vogts have done no physiological experiments personally. But their interest in physiology has not waned. Especially in electroencephalography have they seen a new and fertile soil for investigation. It may perhaps be interesting to recall that the first successful ink-writing electroencephalograph was built by Tönnies in the Vogt institute.

In the consideration of neuropathological problems, attention will be focused on two points: the Vogts' study of extrapyramidal diseases, and their conception of pathoclisis.

Until 1911 the morphological substratum for hypokineses was usually looked for in the pyramidal system, and involuntary movements were explained by irritation of the pyramidal pathway. In 1911, Cécile Vogt described the pathological changes in four cases of *athetose double* and showed that the changes in the nucleus caudatus and putamen were constant in these cases. She called the pathological picture "status marmoratus," a name which, together with that of "Vogt's disease," is now commonly used in the literature. In addition to the description of morphological changes, she discussed some general problems of pathophysiology. She pointed out that neurological symptoms are due not only directly to the extinction of the function of the diseased center, but also to two additional phenomena: dislocation and liberation. The phenomenon of dislocation is the incoordination of normal harmonic cooperation of centers as a result of destruction of one of them; the phenomenon of liberation is a result of the exaggerated function of centers which, under normal conditions, are inhibited by the now diseased center.

In 1920, the Vogts published a comprehensive monograph on extrapyramidal diseases "Zur Lehre der Erkrankungen des striären Systems," which has remained a classic study of the subject. In addition to further cases of status marmoratus, they described the pathological anatomy of 25 cases of extrapyramidal diseases and classified them according to the pathoarchitectonic pictures. Giving an explanation of pathophysiology, the Vogts proposed a scheme of extrapyramidal connections; the general idea of this scheme fits well into the modern conception of these pathways. However, they omitted one important connection, which is rather well established now—the direct corticostriatal pathway. The manner in which they discuss this problem shows well the frankness of their scientific approach. They say:

> We consider the existence of connections between cortex and striatum or pallidum as still unproved. But, as this question is of basic importance, further investigations are urgently needed.

The importance of the Vogts's study of extrapyramidal disease is manifold: They proved the value of pathoarchitectonics in studying problems of localization. They showed that the site of the lesion and the development of the pathological process are closely correlated with clinical symptoms, whereas the minute histological changes are of secondary importance. They demonstrated that processes of different etiology but similar localization can produce similar symptomatology. Finally, they successfully applied the pathological method to the classification of diseases with a clinical classification which was indefinite, and sometimes even misleading. We have only to recall that, only shortly before the discoveries of C. Vogt, some of the hyperkineses with definite anatomicopathological changes were considered to be of a functional character. The Vogts have always believed that the classification of mental disorders will be similarly achieved some day on the basis of pathological anatomy, and they consider their work on extrapyramidal diseases as an introductory step toward this goal. The last conception has not made the Vogts popular among psychiatrists. When, at a scientific convention in 1931 C. Vogt urged the necessity of anatomicopathological studies in psychiatry, one professor of psychiatry left the meeting in protest against such nonsense.

The second point which I should like to mention in connection with the Vogts's pathological studies is their conception of pathoclisis. Though rather obvious to many scientists, this conception has been rejected by others; so I feel justified in outlining it briefly.

The Vogts found that diseases of the nervous system, as well as other biological processes, are confined to structural units. The disposition of a structural unit to undergo pathological changes is called by the Vogts pathoclisis, with the limitation that this disposition is due to the physicochemical properties of the tissue. General pathology furnishes many examples of pathoclisis, such as the peculiar localization of diseases of the skin, infectious diseases and poisonings. In many publications the Vogts have presented examples of pathoclisis in the nervous system, most attention being paid to the cerebral cortex, basal ganglia and thalamus. In "Sitz und Wesen der Krankheiten im Lichte der topistischen Hirnforschung und des Variierens der Tiere," they discussed in detail the changes in the hippocampus and showed that in any given case the identical structural units are diseased both in the main part of the hippocampus and in the uncus. As the uncus and the main part of the hippocampus are not exposed to the same influences of intracranial pressure and blood supply, a purely mechanical explanation of the localization of pathological changes is insufficient.

Another example of pathoclisis, which has been thoroughly analyzed, is the disposition of the pallidum to undergo pathological changes in carbon monoxide poisoning. An attempt made to explain this by the

length and small caliber of the blood-supplying artery cannot be regarded as completely satisfactory, as no evidence is present that the arteria choroidea anterior is the longest and finest of the brain arteries. Moreover, the anterior part of the hippocampus being supplied by the same artery does not succumb to carbon monoxide poisoning. By rejecting the mechanical factor as a cause of diseases limited to a structural unit (their *topische Krankheiten*), the Vogts have not overlooked the fact that a blood vessel, or a system of blood vessels, may show its own form of pathoclisis. For instance, the syphilitic changes in the aorta are localized above the diaphragm, whereas the arteriosclerosis of the aorta is usually found below it. Another example is that of the cases of Bielschowsky and Löwenberg in which the "calcium" deposit was limited to the capillaries of laminas IV b β and IV c of the area striata and ended abruptly at the border of this area.

Before closing this rather summary survey of the Vogts's work, I should like to dwell on one example which shows how the Vogts make use of their brain collection, which is probably unique in the world. About 300 brains, normal or pathological, of illustrious people of art and science, of average people or of criminals, cut serially throughout their entire length and stained for nerve cells and myelin, are immediately available for study. In "*Thalamusstudien*," the Vogts concentrated their attention on the centrum medianum. After having described its normal configuration, they analyzed 11 cases of various lesions in the cortex and basal ganglia. Whereas lesions of the cortex and of the pallidum produce no degeneration in the centrum medianum, the destruction of the striatum is accompanied with cell loss and gliosis. In addition, by selecting suitable cases with only partial destruction of the striatum, they demonstrated that the caudal portion of the putamen receives projection from the lateral, parvocellular part of the centrum medianum, while the nucleus caudatus and the oral portion of the putamen form the end station for the axons of the medial, magnocellular part of the centrum medianum. The manifold and abundant material of the Vogts's collection forms a necessary basis for a study of this type. It took over 50 years to collect this material; its scientific value will last for generations.

It is obvious that what I have said gives only a very general idea of the work of C. and O. Vogt. Much more time, and much more knowledge on my part, would be required to make a more detailed survey. Especially must I say that I completely omitted the Vogts's contribution to the correlation of neurological problems with those of general biology.

The tribute paid to the Vogts on the occasion of their jubilee will not be complete unless we dwell for a moment on the characteristics of their personalities. Their complete devotion of time, interest and financial

means to scientific problems is the most outstanding feature. They live a simple life, following a rather monastic timetable. Everything outside the circle of their interests is consequently eliminated, and little time is left for recreation, in the general sense of the word. For example, during their whole lives, the Vogts have gone only twice to a cinema—both times in a hot foreign country, seeking relief from extreme heat, in some air-conditioned theater. "But," Professor Vogt always adds when conversation turns on this subject, "of course, I have seen scientific movies, and it was a most thrilling experience when I saw on the screen the movements of chromosomes in mitosis."

The Vogts are extremely laborious and diligent. For them no week-ends, no vacation! Once Professor Vogt said to me, referring to one of his previous employees: "That man was terribly lazy. He never turned up for work on Sundays."!

The only matters aside from science which interest the Vogts are social problems and politics. Their sympathies being always with the Social Democrats, they realized from the beginning the menace of the Nazi "Brown Shirts." In 1933, their Institute in Buch was raided by a Nazi gang, under the pretext of searching for concealed Jews and Communists. I do not know whether any Jews or Communists were concealed in the Institute, but I do know that during the latter part of the war two half-Jews, two Poles and one French lady found in the Vogt home not only a refuge, but also kind affection and almost paternal care.

After having expelled the Vogts from their important position in Berlin, the Nazis left them comparatively undisturbed in Neustadt. But mean, petty tricks were still played on them whenever an opportunity presented itself. So, at the beginning of the Second World War, Professor Vogt received unexpectedly an order to join the army. Inasmuch as during the First World War he was not in the army, being too old for active service, he had no previous military training. Consequently, he was called to arms as "Private Vogt." So, being 69 years old, he became probably the oldest, and certainly the most highly educated, private in the German army. Fortunately, after a few weeks he was discharged, the situation being obviously too ridiculous.

Not only was the pseudoscientific basis on which the Nazis tried to build their political theories unacceptable to the Vogts, but it also seemed to them a sacrilege against science. The Vogts were among the few who understood that the only way for Germany to regain her position among the free nations of the world was to lose the war. The Vogts believe in the possibility and the advantages of a one-world government. Intellectually they are the most internationalized persons I ever met in Europe. To hate other people because of their nationality—an attitude so common in Europe—is something beyond their understanding.

I suppose I should be right in saying that the Vogts belong to that group of people who are born ahead of their time. In their scientific, political and social ideas they have always been ahead of their contemporaries. This has sometimes brought them into rather amusing situations. For example, in 1900 C. and O. Vogt presented a paper to be read at the meeting of the Medical Society in Berlin. The paper was accepted, but it was pointed out that Madame Vogt was not supposed to come to the meeting—ladies were not admitted to medical meetings.

In his small booklet on a scientific vocation, Ramón y Cajal mentioned a few examples of married couples who were scientists and who seemed to him to be ideally matched. The Dejerines, the Nageottes, the Curies and the Vogts are named. It is indeed rare to see a husband and wife so perfectly matched in their interests and ambitions, each perfectly the intellectual complement of the other.

Madame Vogt embodies the best of what is known as *l'esprit français*: a vivid temperament, keen intellect, quick understanding and a cheerful sense of humor, which she frequently directs to their own private lives. When I asked her once whether one of their scientific friends worked in neuroanatomy, she answered: "Oh no! He is too ingenious to be an anatomist." Professor Vogt, on the other hand, represents magnificently all those values which have made German science famous throughout the world: His thoroughness, the discipline of his thinking, his perseverance in pursuing his aims—all these are above reproach. He is extremely dynamic, possesses a strong will and the ability to impress, dominate and influence people. It would be difficult to say what part of the total result of the lifework of the Vogts belongs to her and what to him. So it is right that we should always think of them and refer to them as C. and O. Vogt.

The whole lifework of C. and O. Vogt has been based on the assumption that psychological phenomena are correlated with material processes in the brain. We are still very far from even an approximate understanding of these relations; but everything seems to indicate that the Vogts's assumption is correct. In the search for a solution to the most baffling enigma of human nature, we seem to be following the right course.

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PETIT MAL EPILEPSY OCCURRING IN STATUS

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STATUS epilepticus is a well known clinical condition. The closely repeated generalized convulsions constitute a clinical entity known from ancient times. Petit mal status is a condition less widely known. Lennox [1] described three types of petit mal attacks: the akinetic and the myoclonic type and the short stare. Akinetic seizures are transient and characterized by falling if the patient is not supported; the myoclonic type has jerking movements of the body, head or extremities, characteristically at a rate of 3 per second. The short stare type of petit mal is characterized by a brief loss of consciousness without overt movements. The myoclonic petit mal attacks, occurring in rapid sequence over a period of time, as a petit mal status, may be readily recognized. In the akinetic type, the repeated loss of posture is evident. The rapidly repeated short stares are more difficult to recognize as petit mal seizures, and the brief periods of consciousness between attacks may lead to inadequate motor or psychic activity, suggesting a psychomotor seizure. Because adequate reference to petit mal status in the literature is lacking, and since the clinical condition may prove confusing, two cases are reported.

REPORT OF CASES

CASE 1.—*Petit mal status in a woman aged 43. Differential diagnosis included petit mal status, psychomotor seizures and psychoneurotic depression.*

A woman aged 43 began to have petit mal attacks at the age of 11 years and grand mal seizures at the age of 19 years. The petit mal attacks were characterized by "short stares," lasting less than a minute. They had occurred at daily intervals in childhood and had gradually decreased in frequency, and no known petit mal attacks had occurred since the age of 40.

The generalized seizures were preceded by a feeling of "grogginess" and confusion, lasting several days, sometimes associated with headaches and nausea. The seizures began with loss of consciousness, a cry, a fall and tonic and clonic

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1. Lennox, W. G.: The Petit Mal Epilepsies: Their Treatment with Tridione, J. A. M. A. 129:1069 (Dec. 15) 1945.

movements. Tongue biting occurred frequently during seizures. There was no focal aura, and in the postictal state no paralyses or other focal deficit appeared. The generalized seizures occurred approximately every three or four months. The "groggy states" and seizures occurred usually at the menses, and often without a generalized seizure. One of the confused states was described: While she was playing bridge with friends one evening, the "groggy state" began abruptly, followed by inability to concentrate and the necessity of her resting on a sofa for several hours before being clear enough to be taken home.

There was no family history of epilepsy or convulsions in the direct and the collateral lines.

The past history revealed that she was fourth in order of birth. Delivery and development were normal. There were no significant head injuries or serious illnesses. The patient was married and had two children. The husband was deferential and somewhat oversolicitous.

General physical and neurological examinations revealed nothing abnormal. There was no indication of a focal cerebral lesion.

An electroencephalogram taken in June 1948 revealed a well developed 10 per second basic pattern. The cortical activity was equivalent when read to either ear. Overbreathing for three minutes produced short runs, lasting one to four seconds, of bilaterally synchronous bursts of 3 per second wave and spike formations. The record was diagnosed as one characteristic of generalized paroxysmal cerebral dysrhythmia.

Prior to this time, the patient had been treated with phenobarbital, 0.1 Gm., and diphenylhydantoin sodium, 0.1 Gm., per day. There had not been petit mal attacks for 18 months. Generalized seizures constituted the clinical problem. Therefore, diphenylhydantoin sodium, 0.3 Gm. per day, was prescribed. One month later the patient complained of an increase in the "groggy periods" and recurrence of short stares, without major attacks. Trimethadione U. S. P. (tridione®), 0.3 Gm., was added to the medication, and the patient became free from seizures. In October 1948 the patient was admitted to the surgical service of the Jefferson Hospital. A radical mastectomy was performed because of a mass in the left breast. Histologically, this was shown to be a carcinoma. The patient was aware of the implications of the mass in the breast.

On the third postoperative day, the patient became confused. It was not possible to draw her into prolonged conversation; responses to questions were slow, seldom complete and often appeared irrelevant. She was listless and careless as to appearance. There were no myoclonic movements and no postural deficits. Repeated neurological examinations showed a normal status. This condition lasted for 36 hours. The differential diagnostic possibilities entertained at this time were (*a*) reactive depression precipitated by the suspicion of carcinoma, (*b*) psychomotor seizures, (*c*) petit mal status of the short stare type and (*d*) a dreamy state secondary to a lesion of the temporal lobe, perhaps a metastatic carcinoma. An electroencephalogram taken at this time demonstrated that the patient was in petit mal status. Bilaterally synchronous 3 per second wave and spike formations occurred in long bursts and occupied 17 of the 20 minutes employed in the tracing.

After this electroencephalographic study, the dose of trimethadione was increased to 0.6 Gm. per day, and since the major seizures offered a threat, the use of diphenylhydantoin was continued. The petit mal status subsided shortly after the increase in trimethadione. No episodes of "grogginess" or petit mal status have occurred in the intervening nine months, nor have there been any major attacks.

Comment.—It is unusual for petit mal to occur at the age of this patient. The long period of petit mal, of 36 hours, illustrates the difficulty in diagnosis of petit mal status of this type. The symptoms of anxiety and depression were present only as part of the seizure. The aggravation of petit mal seizures by diphenylhydantoin is well illustrated.

CASE 2.—*Grand mal and petit mal seizures and petit mal status clinically suggestive of psychomotor seizures, in a boy aged 14 years.*

C. H. was first seen in the epilepsy clinic of the Jefferson Hospital in October 1945, at the age of 10 years. Petit mal attacks began at the age of 4 years and grand mal seizures at the age of 8 years. The petit mal attacks were of the short stare type, occasionally punctuated by two or three myoclonic jerking movements of the extremities. The attacks lasted from three to four seconds and were associated with loss of consciousness. No irrelevant psychic or motor activity occurred in these attacks.

The major convulsions were preceded by a period of several minutes to several hours of confusion, disrobing, irrelevant productions and walking about with a peculiar steppage gait. From this prodrome, typical generalized tonic and clonic convulsions developed. The prodromal psychomotor-like episodes also occurred without generalized convulsions.

The petit mal attacks occurred twenty times a day. The generalized seizures occurred once a month. The prodromal period, which we interpreted to be psychomotor seizures, occurred without a generalized attack every other month.

The family history showed no case of epilepsy or convulsive disorders in either the direct or the collateral lines. The past history revealed that the patient was third in order of birth. Birth and delivery were normal. He had had a head injury with skull fracture at the age of 8 years (after the onset of petit mal attacks).

General physical and neurological examinations revealed a normal status. Roentgenological studies of the head were interpreted as showing a normal condition.

In the clinic, on October 24, the patient was placed under treatment with diphenylhydantoin sodium, 0.3 Gm. per day. This therapy was directed against his generalized and psychomotor seizures. One week later he was admitted as an inpatient because of a confused state. In this state, he wandered about in hesitant fashion, spoke with hesitation and answered only fragments of questions. When called by name repeatedly, he would reply at intervals of several seconds. Associated with this state were occasional mild bilateral involuntary movements of the extremities suggestive of myoclonic movements. The parents stated that this was the typical preconvulsive state of the patient and the type of attack which we had gathered from the description to be psychomotor in type.

Electroencephalographic study at this time showed preponderantly bilaterally synchronous 3 per second wave and spike formations, occurring in long runs with only short intervening bursts of normal electrical activity. The record could be obtained only over a 230 second interval because of the confused activity of the patient, but the entire record was occupied by the runs of wave and spike formation. Inhalations of 5 per cent carbon dioxide were given, and the petit mal status subsided in 12 minutes. The patient was followed in the epilepsy clinic; he was treated with di-glutamic acid, caffeine, phenobarbital and diphenylhydantoin, which were unsuccessful in controlling the petit mal attacks until Jan. 30, 1946, when trimethadione U. S. P. (3,5,5-trimethyl-2,4-oxazolidinedione

was made available to us. Doses of trimethadione, up to 2.1 Gm. per day, combined with phenobarbital, 0.1 Gm. per day, have succeeded in controlling the seizures. Repeated blood counts have shown no untoward hematologic signs.

Comment.—The necessity of electroencephalographic confirmation in understanding the clinical activity of the petit mal status is well illustrated. The use of inhalation of 5 per cent carbon dioxide was an adjunct in the treatment of the status. The aggravation of the petit mal status by diphenylhydantoin is again illustrated. The seizures in this case have been controlled with trimethadione therapy.

GENERAL COMMENT

The two cases here reported are examples of status epilepticus due to repeated petit mal seizures. The clinical picture during petit mal status is often difficult to recognize. The repeated short attacks with loss of consciousness and with short intervening periods of consciousness disrupt interpersonal contact. The partiality of the contact produces inadequate psychic and motor activity, with fragmentary motivation. The resultant clinical picture can, therefore, resemble a psychomotor seizure or a psychogenic disturbance. In the first case, the patient's age, of 43, and the previous disappearance of petit mal attacks minimized the possible diagnosis of petit mal epilepsy. The presence of carcinoma raised the possibility of a focal cerebral lesion or a reactive depression based on the awareness of the disease. The proper diagnosis was determined only by electroencephalography during the siege of petit mal status. In the second case there was no suggestion of a psychogenic factor, and the patient was known to have both generalized seizures and petit mal attacks. He also had episodes resembling psychomotor seizures occurring prior to the generalized attacks and independently. These were demonstrated by electroencephalograms to be repeated petit mal attacks.

The clinical accounts of these patients indicate that diphenylhydantoin sodium increased the severity of the petit mal attacks. This is a well known clinical fact (Lennox[1]). It is worth comment that the second patient was treated prior to the advent of oxazolidine therapy for petit mal epilepsy, and that in the first case the petit mal attacks had apparently disappeared. In both cases it appears that diphenylhydantoin precipitated the episodes of petit mal status.

Electroencephalography played a major role in the proper diagnosis of petit mal status in these two cases. From the standpoint of clinical observation the differentiation was not sharp, but the brain wave patterns of almost continuous bilaterally synchronous 3 per second wave and spike discharges firmly established the clinical diagnosis. It is a trite observation that in the diagnostic situation presented by these patients electroencephalography during the episodes is essential to the proper diagnosis, and therefore therapy.

When the petit mal attacks are of the akinetic or myoclonic type, the differential diagnosis is less difficult than when attacks of short stares occur in repeated fashion. In the myoclonic type the jerking movements at their 3 per second frequency, and in the akinetic type the repeated loss of posture, are hallmarks of the petit mal nature of the seizure. But in the short stares the absence of overt seizure manifestations makes the diagnosis more difficult.

Petit mal seizures do not tend to produce mental deterioration, and predisposing severe personality disorders were not found in either of these cases. Bridge [2] has noted such disorders in his nine cases.

SUMMARY

Two cases of petit mal status are described. The difficult clinical diagnosis and the value of electroencephalography in arriving at the proper diagnosis are discussed.

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TEMPERATURE REGULATION IN SCHIZOPHRENIA

I. Comparison of Schizophrenic and Normal Subjects
II. Analysis by Duration of Psychosis

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I. COMPARISON OF SCHIZOPHRENIC AND NORMAL SUBJECTS

THE PROBLEM of the etiology and pathogenesis of schizophrenia has been the object of many experimental attacks, including a search for an underlying somatic, or "organic," factor. Those who have made inquiries along this line have brought to light much evidence of physiological abnormality in schizophrenia, associated particularly with the function of the autonomic nervous system.

Hoskins,[1] in 1946, published the results of many years of physiological research, comprising studies of endocrine function, metabolism, circulation and various homeostatic mechanisms. Many other workers have contributed pertinent data to this subject. The over-all impression gained from a review of this literature is that the chief physiological defect in schizophrenia is in the sphere of homeostasis, with diminished adaptability to both endogenous and exogenous stimuli. Dysfunction at the cortical or the hypothalamic level has been implicated most frequently in the explanation of the observed impairment of autonomic function.

In this report, data on temperature regulation are submitted. This material was collected in the course of a more comprehensive study of the clinical, psychological and physiological effects of prefrontal lobotomy in schizophrenic patients (to be published). The observations set forth in this paper were derived from the preoperative survey of temperature regulation in a group of patients involved in this larger study.

Temperature regulation was selected for study because it represents an aspect of homeostatic function which depends on a fine degree of

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1. Hoskins, R. G.: The Biology of Schizophrenia: The Thomas William Salmon Memorial Lectures of the New York Academy of Medicine, New York, W. W. Norton & Company, Inc., 1946.

autonomic integration at the hypothalamic level. Several references to thermoregulation in schizophrenia have appeared in the literature (Freeman,[2] Carmichael and Linder,[3] Freeman,[4] Finkleman and Stephens,[5] Gottlieb and Linder[6] and Cameron[7]). Certain abnormal trends were observed in heat production, in the day to day variation of body temperature and in the response to extremes of heat and cold.

In the present survey emphasis was placed on two aspects of temperature regulation, namely, the diurnal temperature cycle and the temperature response to prolonged thermal stimuli.

CLINICAL SUMMARY OF THE PATIENTS STUDIED

The subjects were 40 schizophrenic patients—38 male and 2 female. The median age was 32 years. The duration of illness at the time of investigation varied from one to eight years, with 80 per cent of the patients falling into the two to five year range. Although all subtypes of schizophrenia were represented in the group, the majority of cases (63 per cent) were of the paranoid type.

THE DIURNAL TEMPERATURE CYCLE

A four day period of study was arbitrarily selected. During this time the rectal temperature of each patient was recorded at four hour intervals throughout the day and night, giving a total of 24 readings. The temperatures were recorded with clinical rectal thermometers calibrated against a standard thermometer in a thermostatically controlled water bath. All readings were made after the thermometer had been in position for five minutes. Care was taken to avoid diurnal temperature studies during the course of infections of the upper respiratory tract and other febrile conditions.

Comparative data from normal subjects were obtained from a series of 10 healthy male volunteers from the graduate school of the university. The median age of his group was 29 years.

The findings for the normal subjects are presented as a composite curve in chart 1. In this graph the solid line joins the means of the individual temperature readings for each of the 24 time points. The

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3. Carmichael, H. T., and Linder, F. E.: Relation Between Oral and Rectal Temperatures in Normal and Schizophrenic Subjects, Am. J. M. Sc. **188**:68-75, 1934.

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6. Gottlieb, J. S., and Linder, F. E.: Body Temperatures of Persons with Schizophrenia and of Normal Subjects: Effect of Changes in Environmental Temperature, Arch. Neurol. & Psychiat. **33**:775-785 (April) 1935.

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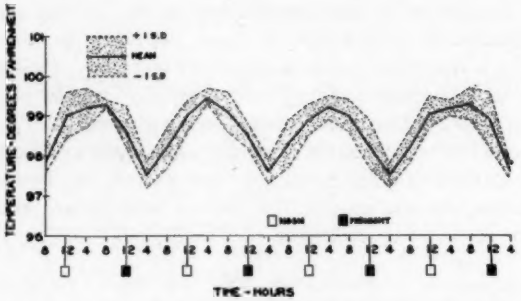

Chart 1.—Mean rectal temperatures for normal controls.

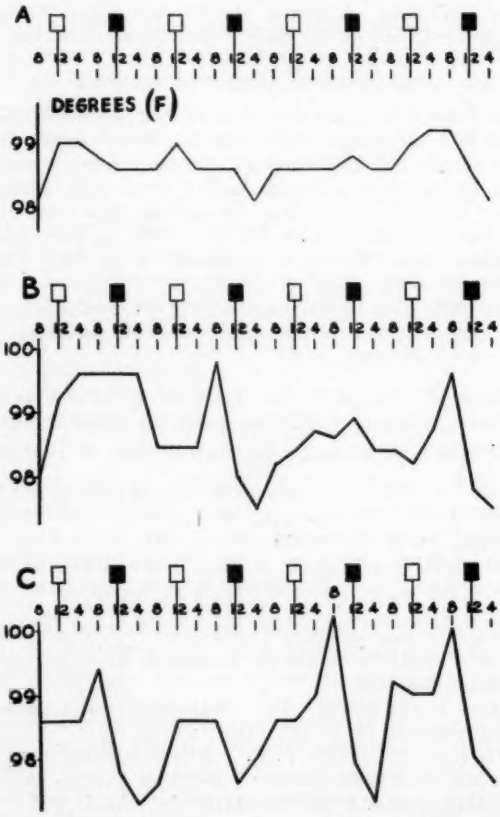

Chart 2.—Individual rectal temperatures for schizophrenic patients. *A*, patient Is.; *B*, patient De., and *C*, patient Be.

dotted lines join the standard deviations about each of the mean values, giving an indication of the degree of scatter. Approximately two thirds of all the temperature readings lie within the dotted area. It is apparent that the normal subjects had uniform diurnal swings of temperature, with a regularly occurring difference between the early morning and the late afternoon readings. There was little variation among the individual members of the group.

A composite graph for the schizophrenic patients is not shown, because the striking variation in the readings of individual patients resulted in a flattened curve, the configuration of which could very well be explained by the individual responses being out of phase with one another. Thus it is necessary to study individual temperature patterns. *A, B* and *C* of chart 2 represent the diurnal temperature cycles of three patients whose temperature patterns illustrate those most commonly encountered in the whole group.

TABLE 1.—*Measurements of the Diurnal Temperature Cycle* in Schizophrenic Patients and in Normal Subjects*

	Patients (40)	Normal Subjects (10)	Significance of Difference
Mean daily range of temperature (degrees F.)	1.5 (± 0.09)†	2.0 (± 0.09)	$p < 0.01$
Day-night temperature differential (degrees F.)	+ 0.5 (± 0.06)	+ 1.1 (± 0.07)	$p < 0.01$
Mean rectal temperature (degrees F.).....	98.5 (± 0.06)	98.7 (± 0.07)	$p < 0.05$

* Group mean values.
† Standard error of the mean.

The curve for patient Is. (chart 2 *A*) exemplifies the flat temperature cycle which was observed in many members of the group. In this patient's record diurnal swings of temperature were greatly reduced. The curve for patient De. (chart 2 *B*) illustrates an irregular type of diurnal cycle which was also encountered frequently. There was a decided difference from one day to another in the breadth of the swing and in the timing of the maximum and minimum temperatures. The curve for patient Be. (chart 2 *C*) reveals another type of abnormality noted among certain members of the group. The curve shows a broad temperature swing based on abrupt changes in temperature, rather than on the smooth progression from maximum to minimum points that was observed with the normal subjects.

The objective analysis of the differences between the normal and the psychotic groups was based on the following measurements of the diurnal cycle: (1) the mean temperature over the four day period; (2) the range of temperatures for each day, from which a mean value was obtained; (3) the day-night differential, i. e., the mean of the day temperatures minus the mean of the night temperatures over the entire four day period.

From the individual means, group means were calculated and compared.[8] These are shown in table 1. (It was not necessary to weight the group means, since all the individual means were obtained from the same number of temperature readings.)

The patients had significantly lower values for the mean daily range of temperature and for the day-night differential than did the normal controls. The mean daily range would be lowered by diminished diurnal fluctuations in temperature. The day-night differential might be decreased either for this reason or because of day to day variations in

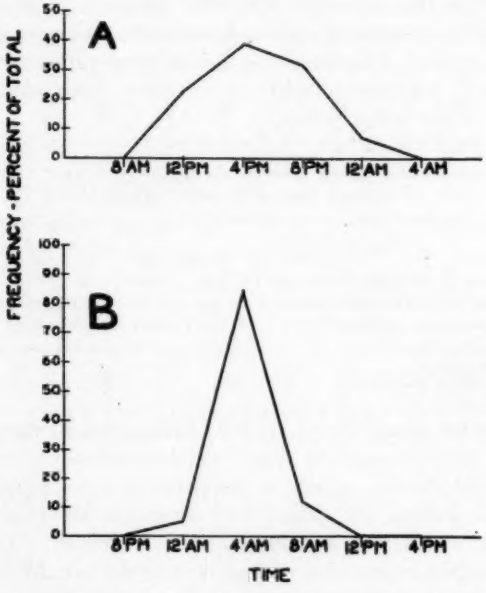

Chart 3.—Times of occurrence of (*A*) maximum temperature and (*B*) minimum temperature for normal controls.

the timing or in the magnitude of the diurnal temperature swing. There was also a small, but significant, difference between the mean rectal temperatures of the two groups, the patients having a lower mean temperature.

The times of occurrence of the daily maximum and minimum temperatures were recorded for each subject. This offered another

8. Differences between means were tested for significance, using the formula based on the standard error of the mean. The p value represents the percentage probability of obtaining purely by chance a difference as great as the one observed. A p value of less than 0.05 was accepted as significant.

means of comparing the diurnal temperature cycles of the schizophrenic patients with those of the normal subjects. Frequency distributions for the times of maximum and minimum temperatures are shown in chart 3, for the normal subjects, and in chart 4 *A* and *B*, for the patients.

In the normal subjects, 4:00 p. m. and 4:00 a. m. were the modal times of occurrence of maximum and minimum temperatures, respectively. There was greater conformity in the time of the minimum temperature than in that of the maximum temperature. The distributions for the patients, although having the same modes as those for the normal subjects, revealed much wider variation in both the maximum and the minimum times. There were a considerable number of minimum temperatures occurring in the late afternoon and of maximum temperatures occurring in the early morning. This supports the observed

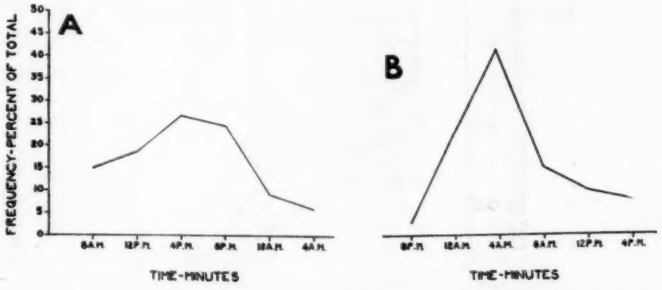

Chart 4.—Times of occurrence (*A*) of maximum temperatures and (*B*) of minimum temperatures for 40 schizophrenic patients.

differences between the patients and the normal subjects in the day-night differential.

RESPONSE OF BODY TEMPERATURE TO HEAT AND COLD

At the completion of the diurnal temperature record, 34 members of the schizophrenic group were studied in hot and cold water baths to determine their reaction to temperature stress.[9] The continuous-flow bath, with the water temperature under thermostatic control, provided a convenient medium for this investigation. Furthermore, it served to minimize the disturbed behavior which many psychotic patients exhibit during such experimental procedures.

The period of observation extended over three hours, two hours in the bath and one hour after removal. The initial temperature of the water was in the neutral zone (96.0 to 96.8 F.), rising gradually for the hot bath to 102 F. and falling for the cold bath to between 60 and 70 F. The temperature extreme was maintained for approximately the last half-hour of the bath period.

9. Six members of the group, because of physical condition or behavior, were unable to be tested in the baths.

After the nude subject had been immersed in the bath to the level of the neck, the tub was covered by canvas straps. Rectal temperatures were taken at 15 minute intervals throughout the three hour period. All readings were made with calibrated thermometers. In taking the readings during the bath, the patient was rolled into the prone position, while an air cushion was slipped under the abdomen to raise the buttocks, only, from the water. The thermometer could thus be inserted without coming in contact with the bath water. During the five minutes required for the reading the canvas cover was replaced over the buttocks to avoid exposure of the body surface. At the completion of the bath, the patient's skin was dried, and he was wrapped in a blanket and allowed to rest on a bed for one hour.

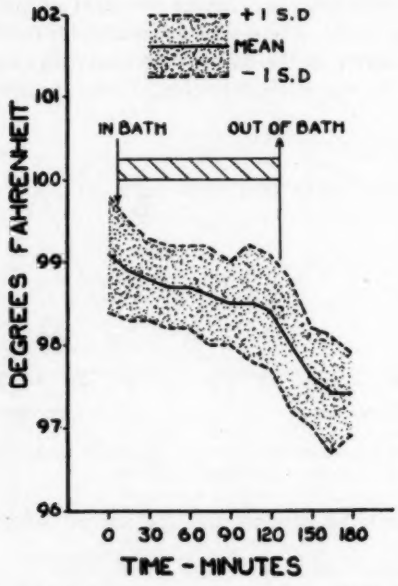

Chart 5.—Mean rectal temperatures for normal controls during and after a cold bath ranging in temperature from 96.8 to 70 F.

A comparable study of normal persons was made on a series of 16 healthy volunteers from the male attendant staff of the hospital. The median age of these subjects was 28 years.

No significant difference was observed between the response of the schizophrenic patients and that of the normal subjects to the hot bath. In both groups the rectal temperature rose gradually, reaching a peak near the termination of the bath and declining after the bath to a point near the original temperature level.

The two groups differed strikingly, however, in their response to the cold bath. The composite curve for the temperature response of the normal subjects is shown in chart 5, each point on the solid line repre-

senting the mean of the individual readings at that time. The rectal temperature fell gradually during the course of the bath and continued to fall for the greater part of the hour following the bath. The rate of decline decreased toward the end of that hour. There was little variation among the individual subjects.

The continued decline in rectal temperature following the cold bath can probably be explained in the following way: On removal of the subjects from the bath a sensation of warmth is evoked by the relatively warm air coming into contact with his cool skin. This sensation induces cutaneous vasodilation, which permits the further loss of heat from the body, resulting in a continued fall in rectal temperature. Toward the end of the hour, the markedly lowered internal temperature brings into

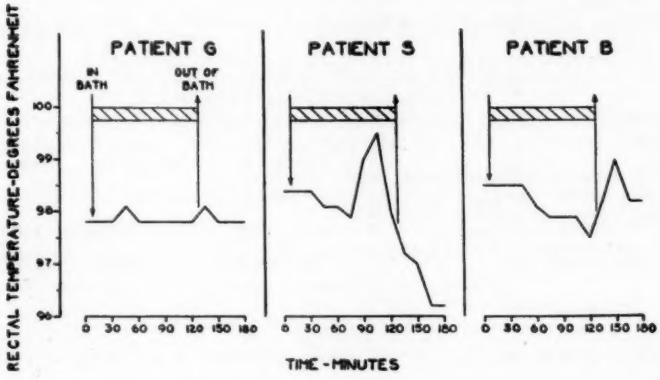

Chart 6.—Individual rectal temperatures of three schizophrenic patients during and after a cold bath ranging in temperature from 96.8 to 70 F.

effect the central mechanisms for heat conservation and further fall in rectal temperature is prevented.

Few of the patients exhibited this type of response to the cold bath. Records for three patients which illustrate well the findings in the whole group are shown in chart 6.

PATIENT B: This patient's curve illustrates a response which was frequently encountered in the schizophrenic subjects. The abnormality lies in the temperature reaction following the bath. Instead of a continued decline in temperature, there was a considerable elevation.

PATIENT G: This patient's response shows in the most exaggerated form a type which was observed in several subjects. Throughout the bath, and afterward, there was no fall in the rectal temperature; in fact, there was a slight elevation at two points in the record.

PATIENT S: This patient's response illustrates another type of abnormality found in certain members of the psychotic group. His response was marked by a

compensatory rise in temperature during the course of the bath, but otherwise it followed the normal pattern.

Statistical analysis of the temperature responses to the cold bath is presented in table 2. It is based on the following measurements:

1. The total change in temperature during the bath—the difference between the preimmersion reading and the reading taken at the end of the bath. 2. The total change in temperature after the bath—the difference between the last reading in the bath and the reading taken one hour after the patient's removal from the bath. 3. The 15 minute change in temperature after the bath—the difference between the last reading in the bath and the first reading after the bath.

The statistical comparison of the normal and schizophrenic groups confirms the observed difference in the temperature reactions after the cold bath. For both the total and the 15 minute change in temperature, the schizophrenic subjects had significantly lower values than the normal subjects. Although some patients were abnormal in their temperature

TABLE 2.—*Measurements of Temperature Response to Cold Bath* in Schizophrenic Patients and in Normal Subjects*

	Patients (34)	Normal Subjects (16)	Significance of Difference
Total change in temperature during bath (F. degrees)	−0.5 (±0.13)	−0.7 (±0.12)	.....
Total change in temperature after bath (F. degrees)	−0.2 (±0.16)	−1.0 (±0.12)	$p < 0.01$
15 minute change in temperature after bath (degrees F.)	−0.02 (±0.09)	−0.4 (±0.10)	$p < 0.05$

* Group mean values.

reaction during the bath, the psychotic group as a whole did not differ significantly from the normal groups in this respect. In the responses to both hot and cold baths there was much greater variation among the individual patients than among the normal subjects.

COMMENT

From the examination of the graphic records, and from the statistical analysis of the measurements pertaining to both the diurnal temperature cycle and the temperature reaction to the baths, it is evident that the schizophrenic patients differed from the normal subjects in several aspects of temperature regulation. The abnormalities observed in the patients were chiefly in the form of irregularity and rigidity. Examples of irregularity were frequent in the diurnal temperature cycle. Pronounced day to day variations in the size of the diurnal temperature range, as well as in the timing of the maximum and minimum temperatures, were noted. Rigidity, or lack of adaptability in thermoregulation, was apparent in the flat diurnal cycle, or in the cycle whose essential flatness was broken periodically by abrupt changes in temperature. The

clearest demonstration of the phenomenon of rigidity, however, was in the reaction to the cold bath in which a steady rectal temperature was maintained after the subject's removal from the bath, in direct contrast to the normal tendency of temperature to fall on contact with the warmer air of the room.

The fact that no differences were found between the responses of the normal and those of the psychotic subjects to the hot bath should not be regarded as conclusive evidence that the response to heat is identical in the two groups. It is known that the hot bath renders inadequate the usual forms of heat loss which operate in a hot air medium. Thus, an element of rigidity in the schizophrenic patient's reaction to heat may well exist, although not revealed by this form of thermal stimulus.

In addition to the abnormalities observed in the individual patients, the psychotic group as a whole showed much greater variation in the temperature measurements of its individual members than did the normal group. Yet in respect to age and daily activity there was little difference in the uniformity of the two groups. Other observers have commented on this divergence among schizophrenic subjects. Freeman and his associates [10] emphasized the marked variation among individual schizophrenic patients in systolic and diastolic levels of blood pressure. McFarland and Goldstein [11] referred to their increased interindividual variations in such biochemical measurements as the blood sugar, nonprotein nitrogen and cholesterol levels.

II. ANALYSIS BY DURATION OF PSYCHOSIS

In the first part of this communication, attention was drawn to certain abnormalities of temperature regulation observed in a series of 40 schizophrenic patients. The marked degree of variation among individual patients was emphasized. Such heterogeneity usually is accepted as an inevitable characteristic of a schizophrenic group. From a statistical standpoint, it suggests that the group observed is not a uniform population but consists of smaller groups differing from each other in temperature regulation through the influence of other variables. Theoretically, many variables might be involved, since schizophrenia is a syndrome rather than a single disease entity. In our group the most obvious measurable factor was that of duration of illness. Therefore a further analysis was carried out on this basis.

The group of 40 patients was divided arbitrarily into two subgroups according to the apparent date of onset of the psychosis.

10. Freeman, H.; Hoskins, R. G., and Sleeper, F. H.: The Blood Pressure in Schizophrenia, Arch. Neurol. & Psychiat. **27**:333-351 (Feb.) 1932.

11. McFarland, R., and Goldstein, H.: The Biochemistry of Dementia Praecox: Review, Am. J. Psychiat. **95**:509-522, 1938.

Group A: Patients whose psychosis at the time of investigation was of four years' duration or less.

Group B: Patients whose psychosis at the time of investigation was of more than four years' duration.

The measurements pertaining to both the diurnal temperature cycle and the responses to heat and cold were then analyzed separately for groups A and B.

COMPARISON OF THE DIURNAL TEMPERATURE CYCLE IN GROUPS A AND B

The mean values for the measurements concerned with the diurnal temperature cycle are presented for groups A and B in table 3. It is

TABLE 3.—*Measurements of the Diurnal Temperature Cycle* in Schizophrenic Patients Grouped According to Duration of Psychosis*

	Group A (24)	Group B (16)
Mean daily temperature range (degrees F.)	1.3 (± 0.09)†	1.9 (± 0.15)‡
Day-night differential (degrees F.)	+ 0.4 (± 0.07)†	+ 0.8 (± 0.12)§

* Group mean values.
† Significant difference from normal.
‡ No significant difference from normal.
§ Difference from normal approaching significance ($p = 0.06$).

TABLE 4.—*Measurements of Temperature Response to Cold Bath* in Schizophrenic Patients Grouped According to Duration of Psychosis*

	Group A (19)	Group B (15)
Total change in temperature during bath (degrees F.)	— 0.5 (± 0.18)†	— 0.4 (± 0.17)†
Total change in temperature after bath (degrees F.)	— 0.1 (± 0.22)‡	— 0.5 (± 0.23)§
15 minute change in temperature after bath (degrees F.)	+ 0.1 (± 0.13)‡	— 0.2 (± 0.11)†

* Group mean values.
† No significant difference from normal.
‡ Significant difference from normal.
§ Difference from normal approaching significance ($p = 0.056$).

evident from this table that the two groups of patients differed significantly in the mean daily range of temperature and in the day-night differential. The group with earlier psychoses had low values for both measurements, while patients with more chronic psychoses had higher values, differing from normal subjects only in the size of the day-night differential. (This difference was of borderline significance.)

COMPARISON OF THE RESPONSES TO THE BATHS IN GROUPS A AND B

No significant difference was found between groups A and B in the temperature response to the hot bath. The statistical analysis of the measurements of temperature change during and after the cold bath is

given in table 4. This table shows that group A had significantly less fall in temperature after the cold bath than did group B. The former differed significantly from the normal in both measurements, while the latter differed from normal only in the total change in temperature after the bath. (This difference, itself, was of borderline significance [p=0.056].)

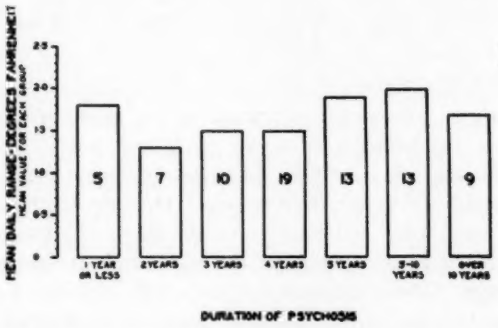

Chart 7.—Mean daily range in temperature for schizophrenic patients grouped according to the duration of their psychoses. The numerical insert indicates the number of patients in each group.

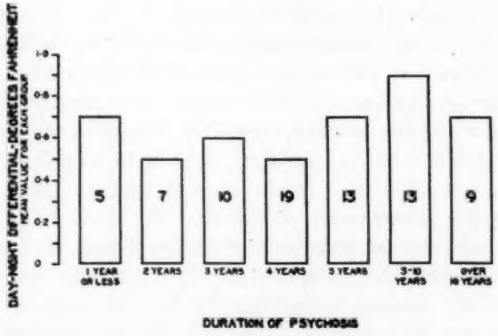

Chart 8.—Day-night temperature differentials for patients grouped according to the duration of their psychoses. The numerical insert indicates the number of patients in each group.

FURTHER INVESTIGATION OF THE DURATION FACTOR

The observed relation between thermoregulatory function in schizophrenia and the duration of illness is based on data that were limited with respect to the range of duration. In the group of 40 patients there were few with very early schizophrenia (that is, of less than two years'

duration), while there were no patients with psychoses of more than 10 years' duration. Thus, no information was provided as to the status of temperature regulation in patients at these two extremes of the duration range.

Investigation of a larger series of schizophrenic patients, therefore, was indicated. The diurnal temperature cycle was studied in 36 additional patients, including those with very early and very chronic psychoses. These data were combined with those from the original group of 40 patients. The resulting sample permitted a more adequate comparison of temperature control in the various stages of the psychosis.

The analysis according to duration of the psychosis for the mean daily range of temperature is shown in chart 7 and for the day-night differential in chart 8. For both these measurements the lowest values (or the greatest difference from normal) are seen in the groups with illnesses of two, three and four years' duration. Contrastingly higher values are noted in the groups at the early and late extremes of the duration range. These observations have been confirmed statistically. It was found that the two to four year group differed significantly from the normal in both measurements, while the early and late groups differed from the normal only in the day-night differential.

COMMENT

In the data from this series of patients one has an indication that abnormalities of temperature regulation are most prominent in schizophrenic patients whose illnesses are in the intermediate range of duration (from two to four years). Patients in the more chronic stages of the disease did not deviate as widely from the normal in their temperature regulation. Manifestations of rigidity, particularly, were less conspicuous in these patients. The size of the diurnal temperature range, which reveals well the phenomenon of rigidity, was normal in the chronic group. The temperature reaction after the cold bath, another index of rigidity in thermoregulation, was closer to that of the normal in these patients. With respect to irregularity in temperature regulation, measured best by the day-night differential, the chronic group was seen to occupy a borderline position, differing still from the normal, yet closer to the normal than the group with psychoses of intermediate duration.

The schizophrenic patients with very early psychoses resembled the chronic group from the physiological standpoint. Abnormality of temperature regulation was minimal, existing chiefly in the form of diurnal irregularity. However, it must be emphasized that this group was very

small, and therefore definite conclusions as to the status of temperature regulation in early schizophrenia cannot be drawn from the data.

In considering differences in temperature regulation which appear to be associated with duration of psychosis, one must not neglect the factor of age, for in general age and chronicity of psychosis are positively related. To determine the possible influence of age on the temperature measurements, correlation coefficients were calculated for age and for each of the measurements. There were no significant correlations, except between age and the absolute level of rectal temperature, in which case a significantly negative correlation was obtained ($r = -0.35$ [± 0.10]). For this reason, differences in mean rectal temperature according to duration of psychosis were not considered.

The demonstration of abnormalities of temperature regulation in schizophrenia with variations in the degree of abnormality in different stages of the illness suggests an interesting parallel between the clinical and the physiological course of the psychosis. The clinical picture is one of a disease which usually begins insidiously, progresses to a stage of maximal behavior disturbance, with severe emotional upheaval, and ultimately levels off into a phase which has been variously described as flattening, deterioration or emotional blunting. The pattern of homeostatic autonomic function, as illustrated here by temperature regulation, would seem to pass through comparable stages. During the first year of recognized illness the disturbance of temperature regulation is minimal, becomes severe during the acute, intermediate phase of the psychosis and then recedes as the illness progresses toward chronicity.

Further information concerning homeostatic function in schizophrenia has been derived from a study of temperature regulation in this same group of patients after the operation of prefrontal lobotomy. A report of this work will be published separately.

SUMMARY OF PARTS I AND II

This investigation has been concerned with homeostatic function of the autonomic nervous system in schizophrenia. Temperature regulation was selected for study as a suitable example of homeostatic activity.

The investigation was divided into two parts. In the first, a comparative study of the diurnal temperature cycle and the temperature response to heat and cold was made in a group of normal subjects and in a series of 40 schizophrenic patients prior to the operation of lobotomy.

In the second part, the status of temperature regulation according to the duration of the psychosis was analyzed. For the analysis of the diurnal temperature cycle, a larger series of patients was studied, in order to include patients at the two extremes of the duration range.

The findings in this investigation have indicated that homeostatic autonomic function, if adequately represented by temperature regulation, is disturbed in schizophrenia, particularly during that period in which the psychosis, although definitely established, is relatively early and acute.

The interpretation of these results is discussed, the apparent relation between the course of the psychic and that of the physiological characteristics of the disease being stressed.

EFFECT OF STIMULATION OF AREA 4s ON FASCICULATIONS

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THE EFFECT of the stimulation of certain suppressor areas on muscular activity has been well demonstrated. Dusser de Barenne and McCulloch [1] showed that stimulation of area 4s causes cessation of movements and relaxation of contracted muscles. Magoun and Rhines [2] found that stimulation of the ventromedial portion of the bulbar reticular formation inhibited the reflex activity of animals decerebrated above the bulb. McCulloch, Graf and Magoun [3] showed that stimulation of area 4s fires the bulbar reticular formation. There is therefore a suppressor mechanism from area 4s, mediated through the bulbar reticular substance, which affects the motoneuronal pool of the spinal cord. Denny-Brown and Pennypacker [4] stated the belief that fasciculations arise as a result of a pathological process in the anterior horn cell. The work of Forster and Alpers [5] and Forster, Borkowski and Alpers [6] has indicated that the site of origin of fasciculations is not the anterior horn

This study was aided by a grant from the National Foundation for Infantile Paralysis.

From the Department of Neurology, Jefferson Medical College of Philadelphia.

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cell but the myoneural junction. Since the previously outlined suppressor system has an inhibiting effect on the activity of the anterior horn cell, the present investigation was undertaken to determine whether stimulation of area 4 s would suppress fasciculations.

METHOD

These experiments were carried out on four monkeys (Macaca mulatta). All were anesthetized by the injection of diallylbarbituric acid (dial®) with urethane,[7] in doses of 0.45 to 0.5 cc. per kilogram of body weight, half the dose being administered intraperitoneally and the other half intramuscularly. The cerebral hemispheres were widely exposed in all four animals. Bipolar silver–silver chloride electrodes were placed at various places on the cortex, and the activity was recorded by means of an eight channel, condenser-coupled amplifier with an ink-writing oscillograph (Grass). The motor cortex was explored with a Goodwin stimulator until a region was found which yielded a discrete response, such as flexion or adduction of the contralateral thumb. Bipolar recordings were obtained from pairs of needle electrodes placed in muscle contracting in response to the cortical stimulation. In addition, pairs of needles were inserted into other muscles of the arm and forearm for control readings. Area 4 s was mapped by strychninization and by electrical stimulation. The technic used was that described by Dusser de Barenne and consisted in applying strychnine sulfate by pledget to the cortex. When the strychninized cortex was suppressor in type, the cortical electrical activity was noted to decrease in amplitude after four to 10 minutes, and repeated electrical stimulation of the motor area at one minute intervals failed to evoke a previously elicited response. Similar results were obtained by electrical stimulation of the suppressor area. Fasciculations were produced by the injection of 1 to 3 cc. of neostigmine methylsulfate intraperitoneally. These were recorded by the ink-writing oscillograph. The area 4 s was then stimulated electrically. After a suitable interval, acetylcholine chloride was applied to area 4 s in 10 and 20 per cent solutions by means of filter paper pledgets measuring 1 by 1.5 to 2 mm., with production of acetylcholine discharges. The pledgets were then removed, and the cortical activity was allowed to return to normal. Strychnine sulfate, 3 per cent solution, was then applied by means of similar pledgets, and typical strychnine spikes were produced. The order of these applications varied with the different animals, but in all cases the effect of one means of stimulation was permitted to clear up, as indicated by the return of the electrical activity to normal, before the next agent was applied. In one animal sodium cyanide was applied to the suppressor area by means of the filter pledgets described above, permanently abolishing its electrical activity. In another animal sodium cyanide was applied to the motor area previously mapped electrically, abolishing its electrical activity.

RESULTS

The neostigmine methylsulfate administered intraperitoneally produced generalized fasciculations of skeletal muscle. The activity of these muscles was recorded as single spikes or short bursts of spikes by the

7. Solution dial® with urethane was generously supplied by Ciba Pharmaceutical Products, Inc., Summit, N. J.

ink-writing oscillograph. Electrical stimulation of the suppressor area produced cortical suppression but had no effect on the fasciculations, either as noted directly or as recorded by the oscillograph. The effect of acetylcholine on suppressor areas will be reported in another paper, but no effect of acetylcholine activation on fasciculations was noted, during either the initial "release" phase or the subsequent suppression phase. Strychninization of the suppressor area had no effect on the fasciculations, although suppression of the cortical activity was recorded. When the activity of the suppressor area was abolished by sodium cyanide, no alteration in the fasciculations was noted. Destruction of the electrical activity of the motor region by means of sodium cyanide was without effect on the fasciculations.

COMMENT

In view of the clinical relationship between anterior horn cell disease and fasciculations, it has been assumed that the site of fasciculations is in the anterior horn cell. Several authors [8] have shown, however, that spontaneous muscular fasciculations are not affected by spinal anesthesia or peripheral nerve block, and in another study [6] we reported the presence of fasciculations after denervation of fasciculating human skeletal muscle. In addition, it has been shown that physostigmine and neostigmine, drugs which act at the myoneural junction, produce fasciculations.[9] Curare also abolishes fasciculations, again by its effect at the myoneural junction. The present investigation was undertaken to determine whether inhibition of the activity of the anterior horn cell by stimulating a suppressor area would abolish the fasciculations. Several methods of stimulation were attempted, including strychninization, electrical stimulation and acetylcholine activation, all of which failed. This result cannot be construed as definite proof that fasciculations are not related to the anterior horn cell because the mechanism of suppression is not completely understood. However, it adds another bit of evidence to indicate that the origin of fasciculations must be peripheral to the anterior horn cell. It was noted that stimulation of the suppressor area caused cessation of restless skeletal muscular movements but the fasciculations continued unchanged.

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8. Forster and Alpers.[5] Grund, G.: Über die Entstehung der fibrillären Muskelzuckungen bei spinalen Amyotrophien, Deutsche Ztschr. f. Nervenh. **145**:99, 1938. Russel, C. K.; Odom, G., and McEachern, D.: Physiological and Chemical Studies of Neuromuscular Disorders, Tr. Am. Neurol. A. **64**:120, 1938. De Jong, H., and Simons, D. J.: A Comparative Study of Fibrillation and Tremor, J. A. M. A. **118**:702 (Feb. 28) 1942.

9. Langley, J. N., and Kato, T.: The Physiological Action of Physostigmine and Its Action on Denervated Muscle, J. Physiol. **49**:410, 1915.

SUMMARY AND CONCLUSIONS

Electrical stimulation, acetylcholine activation and strychninization of area 4 s had no effect on the incidence of fasciculations of skeletal muscle induced by parenteral injection of neostigmine methylsulfate.

Abolition of the electrical activity of area 4 s and of the motor area also caused no alteration in the incidence of the fasciculations.

Therefore, activation of the suppressor area, with its inhibitory action on the anterior horn cell, has no effect on fasciculations.

BRAIN REVASCULARIZATION AFTER CAROTID-JUGULAR ANASTOMOSIS ASSESSED BY ANGIOGRAPHY

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BECK, McKhann and Belnap[1] made a noteworthy attempt to increase the vascularization of the brain in patients with mental retardation, convulsive disorders and various types of sensory and motor defects. These investigators established an arteriovenous fistula between the common carotid artery and the internal jugular vein, thereby converting the vein into an arterial channel. They chose the right side for the anastomosis, because a colored mixture injected into the right internal jugular vein in cadavers "filled the superior sagittal sinus and all of its visible branches." They concluded:

> . . . The right jugular vein drains the cerebral cortex and that [blood] reaching the left jugular comes from the deeper portions and cerebellum. . . . Operation upon the right side would contribute the majority of blood to the cortex and also significant amounts to the deep circulation.

They operated on 11 patients and reported their results in four, stating that "although the postoperative follow-up is limited to one, three, and five months, benefit has been obvious. We believe that this procedure represents the first successful attempt at correction of mental retardation on an organic basis."

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1. Beck, C. S.; McKhann, C. F., and Belnap, W. D.: Revascularization of the Brain Through Establishment of a Cervical Arteriovenous Fistula: Effects in Children with Mental Retardation and Convulsive Disorders, J. Pediat. **35**:317-329, 1949.

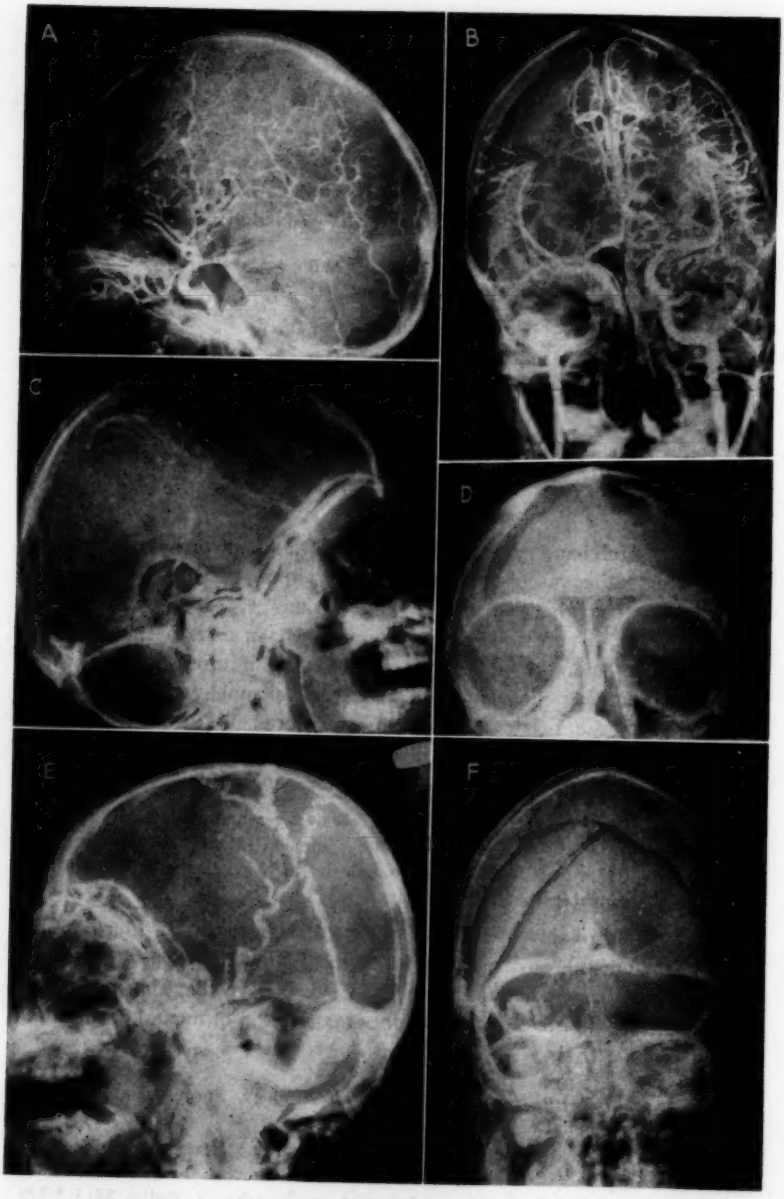

Figure 1

(See legend on opposite page)

Our purpose in the present study was to assess the value of the operation by means of cerebral angiography, which, it was hoped, would provide information concerning the redistribution of blood flow after an arteriovenous fistula had been established between the right common carotid artery and the internal jugular vein. The basis of the present report was three mentally and physically retarded children. In accordance with the technic described by Beck, McKhann and Belnap, an arteriovenous fistula was created. Cerebral angiography with injection of a 35 per cent solution of iodopyracet (diodrast®) was performed before and at least once after operation. In addition, we were able to demonstrate the mechanism involved in the production of proptosis, one of the serious complications of this operation.

REPORT OF CASES

CASE 1.—S. D., a 3 year old boy, was born of a primiparous woman after 22 hours of labor and a difficult forceps delivery. There were persistent rigidity dating from birth and infrequent purposeless voluntary movements. He could neither talk nor sit up and had no control of bowel or bladder function. He could swallow soft food without difficulty, but solid food caused gagging.

EXPLANATION OF FIGURE 1

Case 1.—*A*, right lateral cerebral angiogram that was taken immediately after the injection of 10 cc. of 35 per cent iodopyracet solution. This, the first film in the series, shows excellent filling of the internal carotid and anterior and middle cerebral arteries. The medium has also filled some of the extracranial arteries.

B, anteroposterior angiogram taken immediately after the injection of 10 cc. of the iodopyracet solution. The left common carotid artery had been compressed just before the injection. There is excellent filling of the right anterior and middle cerebral arteries, as well as visualization of the left anterior and middle cerebral arteries. The anterior communicating artery is well filled, and both common carotid arteries are opacified.

C, right lateral angiogram taken three seconds after the injection of 12 cc. of the iodopyracet solution, showing most of the contrast medium in the transverse sinus. The torcula Herophili is opacified. Some dye is seen in the cerebral veins. The entire series failed to reveal dye in the cerebral arterial circulation.

D, anteroposterior angiogram immediately after the injection of 12 cc. of the iodopyracet solution. The opaque medium is present in both the right and the left transverse sinuses.

The angiograms shown in figure 1 *C* and *D* were made three weeks after the establishment of the anastomosis between the right common carotid artery and the internal jugular vein.

E, right lateral angiogram made three months after the establishment of the arteriovenous anastomosis. This angiogram was made three seconds after the injection of 15 cc. of the iodopyracet solution. The medium is present in the transverse sinus. Tortuous and dilated veins can be seen in the scalp over the frontal and parietal regions, and a rich venous plexus is visible at the base of the skull. The right internal carotid artery is not opacified. Swelling of the soft tissue of the scalp can be seen.

F, anteroposterior angiogram made three seconds after injection of 15 cc. of iodopyracet solution. The dye has traversed the right transverse sinus and entered the left transverse sinus. The superior sagittal sinus is not opacified except for a short distance immediately above the confluence of the sinuses. A large venous plexus is seen beneath the right transverse sinus. This study was made immediately after the right lateral angiogram (*E*).

Physical examination revealed an irritable child, who held his mouth open, with tongue protruded and drooling saliva. His body was fairly well developed, but his head was rather small. There was generalized rigidity, with only slight voluntary movement of his limbs. He could roll over from the prone to the supine position but not back again.

Examination of the urine, blood and cerebrospinal fluid showed no pathologic change. Roentgenographic examination of his skull showed no gross bony deformity other than union of all the sutures of the cranium. A pneumoencephalogram revealed diffuse cerebral atrophy. On Jan. 25, 1950, cerebral angiograms were made in the right lateral, the left lateral and the anteroposterior position; 10 cc. of the 35 per cent iodopyracet solution was injected for each projection. No visible alteration in the vascular pattern was observed (fig. 1 *A* and *B*).

Two days later, with the child under general anesthesia, a side to end anastomosis between the right common carotid artery and the proximal stump of the right internal jugular vein was made. The blood pressure rose from the preoperative level of 120/80 to 150/110. After three days the blood pressure became stabilized at its preoperative level. The pulse rate was unaffected by the operation.

On February 3 the arteriographic studies were repeated, using the same technic. The cerebral vessels were not visualized. On February 13 the site of anastomosis was exposed. The common carotid artery and the internal jugular vein were patent, but the site of anastomosis appeared to have been narrowed. A new fistula was created between these vessels about 1 cm. above the previous site of anastomosis. The incisions in the blood vessels were 6 mm. in length, so that after the vessel walls were sutured together the opening measured approximately 4 mm. in length.

On February 20 cerebral angiographic studies were again performed, with the patient under general anesthesia. This examination revealed that the blood traversed the internal jugular vein and the transverse sinuses. There was very little filling of the intracranial arterial tree. The injection was repeated twice, with similar results. On both examinations the tip of the needle was just below the site of anastomosis.

On March 6, 21 days after the new anastomosis had been made, angiograms were taken in the same way. Good filling of the right internal jugular vein and the right transverse sinus followed the injection. Moreover, the left transverse sinus and the left internal jugular vein were visible (fig. 1 *C* and *D*). A few vessels extending from the transverse sinus into the inferior portions of the occipital and posterior temporal lobes were visible. Very little filling of the intracranial arterial tree was present.

The child was discharged from the hospital on March 13 and was readmitted for angiographic studies on May 15. His mother stated that no improvement in his physical or mental condition had occurred since operation. Examination confirmed this opinion. Some puffiness of the face and neck, as well as slight but definite proptosis of the right eye, had appeared in the two months before the child's readmission to the hospital.

On May 15, three months after the establishment of the fistula between the carotid artery and internal jugular vein, cerebral angiograms were again taken. The needle tip was placed in the common carotid artery several centimeters below the site of anastomosis. Fifteen cubic centimeters of the iodopyracet solution was injected for lateral and anteroposterior angiograms. There was excellent visualization of both transverse sinuses (fig. 1 *E* and *F*). The superior sagittal sinus was by-passed. A large plexus of dilated veins was visible around the base of the skull, being more pronounced on the right side. The superficial temporal veins were distorted and dilated. Considerable swelling of the soft tissues of the scalp was observed. The intracranial arterial system could not be seen.

CASE 2.—J. M., a 12 year old girl, was born of a primiparous mother after a difficult labor of 48 hours and a forceps delivery. The child appeared normal at birth, but development was very slow. She was barely able to raise her head at the age of 17 months and presented generalized rigidity. At the age of 9 years bilateral resection of the head of the caudate nucleus was done at another hospital. Her condition did not improve.

Examination revealed a frail child lying in bed with her thighs and knees flexed and strongly adducted. She was unable to speak except for an indistinct "yes" and "no." She appeared to understand some conversation. There were a marked generalized increase of tone and feeble voluntary movements of the lips, fingers and legs.

Laboratory studies of the urine, blood and cerebrospinal fluid gave normal results. Roentgenographic examination of the skull showed an old craniotomy

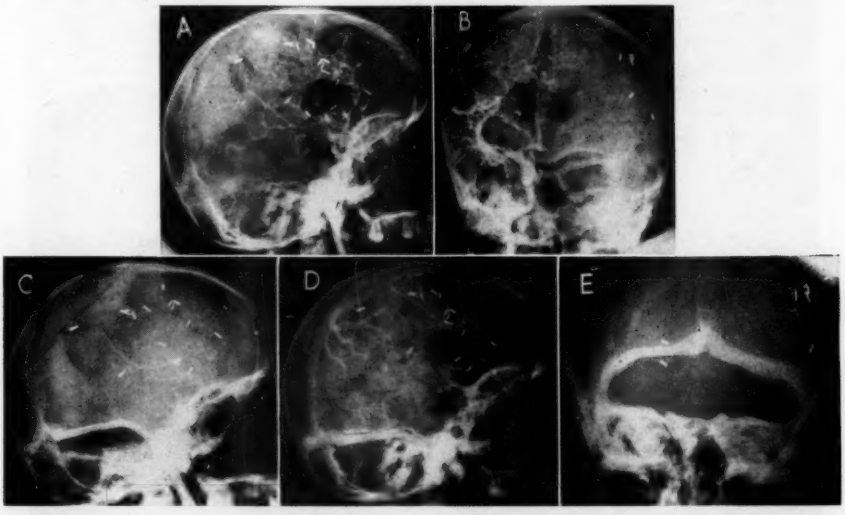

Fig. 2 (case 2).—*A*, preoperative right lateral cerebral angiogram made immediately after the injection of 10 cc. of the iodopyracet solution. The internal carotid artery is normal. The anterior and middle cerebral arteries appear normal. The silver clips were used in a previous operation. A pneumoencephalogram had been made a few hours before the angiogram.

B, right anteroposterior angiogram made immediately after injection of 10 cc. of the iodopyracet solution, revealing a normal vascular pattern.

C, right lateral angiogram made eight days after the establishment of an anastomosis of the right internal jugular vein and common carotid artery. The roentgenogram was made immediately after the injection of 12 cc. of the iodopyracet solution. Most of the opaque medium has entered the right, as well as the left transverse sinuses. A small amount is present in the superior sagittal sinus and the internal carotid, anterior and middle cerebral arteries.

D, angiogram made three seconds after injection of iodopyracet solution and eight days after establishment of the arteriovenous anastomosis, revealing the venous phase. Iodopyracet (12 cc. injected) is present in the transverse sinuses, the superior sagittal sinus and its tributary cerebral veins.

E, anteroposterior angiogram in the same series as *C* and *D*. The iodopyracet (12 cc. injected) fills both the right and the left transverse sinus, the superior sagittal sinus being bypassed in this circuit.

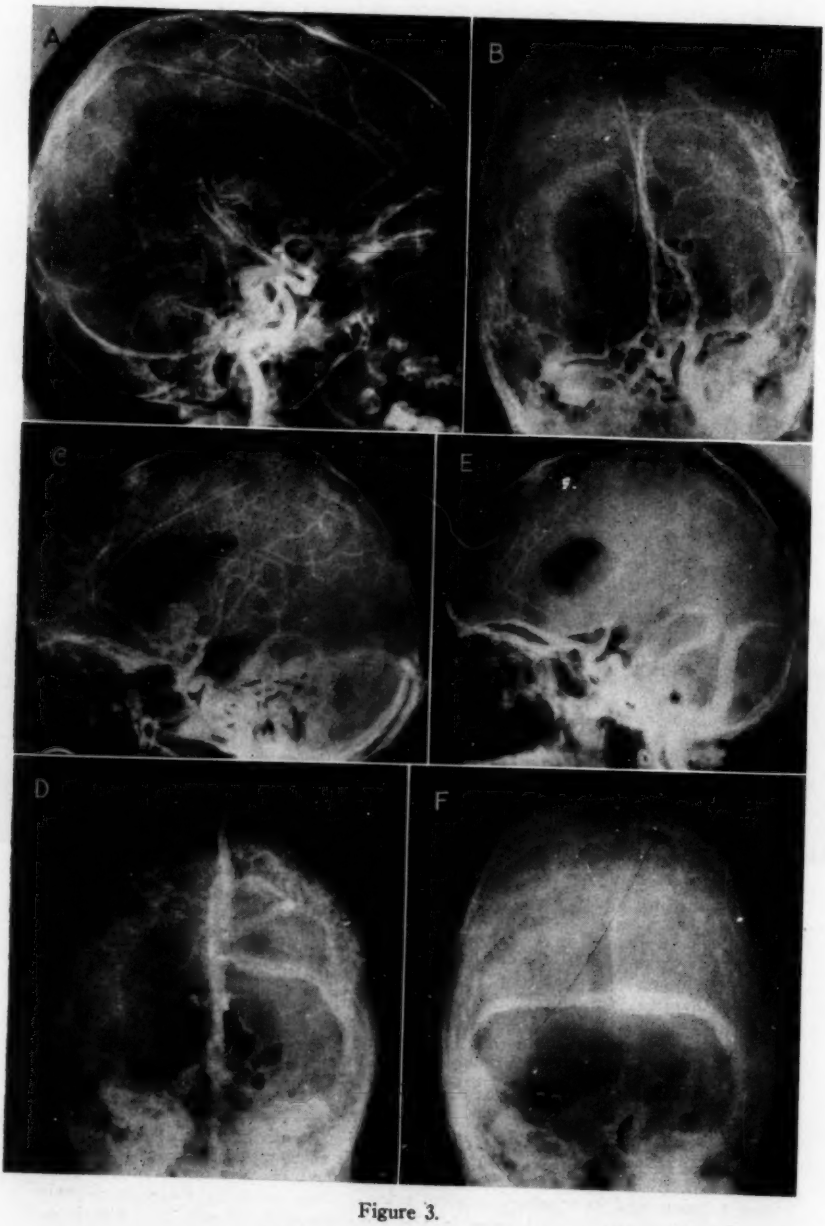

Figure 3.

(See legend on opposite page)

scar in the frontoparietal area bilaterally and silver clips marked the site of the previous operations. Pneumoencephalographic studies revealed cerebral atrophy. Cerebral angiograms were made in the right lateral and anteroposterior positions, using 10 cc. of iodopyracet injection U. S. P. The vascular patterns were not abnormal (fig. 2 *A* and *B*).

On March 28, 1950, with the patient under general anesthesia, an anastomosis was made between the right common carotid artery and the right internal jugular vein. The incision in each vessel measured 5 mm. in length. Before operation the blood pressure was 100/70; after operation it varied from 116/90 to 108/64. The pulse rate increased from 88 before operation to 132 after operation. After 30 hours, however, it returned to 88 and remained there.

Cerebral angiographic examination was repeated on April 5, 12 cc. of the iodopyracet solution being injected below the site of anastomosis. Most of the contrast medium traversed the transverse sinuses from right to left and a small amount entered the superior sagittal sinus. A small quantity of dye entered the internal carotid artery. Drainage of the iodopyracet solution down the left internal jugular vein could be demonstrated in the anteroposterior view (fig. 2 *E*). The amount of iodopyracet solution entering the cerebral arterial circulation was greatly diminished as compared with that seen in the preoperative angiograms. The venous drainage phase of the injection is well shown in figure 2 *D*.

The patient was discharged from the hospital on April 9. Her condition was unchanged.

She was readmitted to the hospital for arteriographic studies on May 9. The examination was repeated 42 days after creation of the anastomosis between the carotid artery and the jugular vein; 15 cc. of the iodopyracet injection was given for the lateral views and for the anteroposterior projections. The needle was placed

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EXPLANATION OF FIGURE 3

Case 3.—*A*, preoperative right lateral cerebral angiogram that was made immediately after the injection of 10 cc. of iodopyracet solution (35 per cent). The internal carotid artery is normal. The anterior cerebral artery is displaced forward, and its callosal branch is elevated by the dilated lateral ventricles. The middle cerebral artery appears normal.

B, anteroposterior angiogram in the same series as *A*. Some of the iodopyracet solution has entered the cerebral circulation on the left side. A pneumoencephalogram, made a few hours before the angiogram revealed hydrocephalus.

C, postoperative right lateral angiogram made immediately after the creation of a fistula between the right carotid artery and the jugular vein and immediately after the injection of 15 cc. of iodopyracet solution, with the tip of the needle in the common carotid artery just distal to the fistula. The number of opacified vessels from the anterior and middle cerebral arteries appears to be greater than that seen in *A*, probably because a greater amount of contrast medium was injected. The dye has also entered the transverse sinus.

D, anteroposterior angiogram with the needle in the common carotid artery just distal to the fistula. The exposure was made immediately after the injection of 15 cc. of iodopyracet solution (35 per cent). The superior saggital sinus and the right transverse sinus are opacified. Radiopaque material is also seen on the left side.

E, right lateral angiogram made immediately after operation with the tip of the needle proximal to the anastomosis, showing the iodopyracet (15 cc. injected) entering the transverse sinus, while a small amount has entered the internal carotid artery. The opacified vessels are fewer than those in *C* and *D*.

F, postoperative anteroposterior angiogram taken with the needle tip proximal to the anastomosis. Very little iodopyracet has entered the arterial circulation. The main stream traverses the right and left transverse sinuses.

just proximal to the fistula. Almost all of the dye entered the right internal jugular vein and then entered the right transverse sinus, whence it crossed to the left transverse sinus and left the skull through the left internal jugular vein. The result was the same even when the tip of the needle was placed in the lumen of the common carotid artery above the fistula. Very little dye entered the intracranial carotid circulation, and very little of it reached the medial longitudinal sinus. Few dilated tortuous veins were seen at the base of the skull.

CASE 3.—D. S., a 14 year old boy, was delivered by forceps of a primiparous mother after a seven months' gestation. His weight at birth was 3 pounds 14 ounces (1,704 Gm.). At 4 months of age he weighed 14 pounds (6,350 Gm.), and his parents observed that he held his head up and crawled. When he was 9 months old, however, it was recognized that he was physically and mentally retarded. He could not sit up and took no notice of his surroundings. His generalized spasticity became more evident, and he had to be spoon fed.

Examination revealed an unresponsive child lying in a fixed position with his mouth open. The upper limbs were flexed at the elbows and wrists, and the lower limbs were flexed at the hips and knees. The extremities could not be extended because of contractures at the elbows and knees. There was generalized hyperreflexia. He was unable to talk, sit up or walk.

The urine, blood and cerebrospinal fluid were normal. Roentgenographic examination of the skull showed no gross abnormalities, but pneumoencephalographic studies revealed pronounced dilatation of the ventricular system and a considerable amount of gas in the subarachnoid space.

On April 17, 1950, a right cerebral angiogram was made under direct vision; 10 cc. of 35 per cent iodopyracet solution was injected, revealing some elevation of the anterior cerebral artery secondary to the dilatation of the lateral ventricles. The venous return by way of the medial longitudinal sinus and the right transverse sinus was clearly shown (fig. 3 *A* and *B*).

On April 20, with the child under general anesthesia, an anastomosis was made between the right common carotid artery and the right internal jugular vein. The incision in each of these vessels measured 6 mm. Angiograms were then made before the wound was closed. On this occasion, 15 cc. of the iodopyracet solution was injected, with the point of the needle at the cranial end of the anastomosis. The circulation in the internal carotid artery was well shown (fig. 3 *C*). The number of arterial channels visualized was somewhat greater than that seen in the preoperative angiograms, probably owing to the greater amount of iodopyracet injected. The right internal jugular vein, the right transverse sinus and the superior sagittal sinus were opacified. The needle was then reintroduced so that its point lay in the common carotid artery 3 cm. proximal to the fistula, and the angiographic examination was repeated twice, using 15 cc. of the iodopyracet solution for each injection. Both studies showed passage of the iodopyracet up the right internal jugular vein and the right transverse sinus, thence to the left transverse sinus and out of the skull through the left internal jugular vein (fig. 3 *F*). The superior sagittal sinus was not visible, and relatively little dye entered the internal carotid artery.

The blood pressure before operation was 100/76; after operation it varied from 100/60 to 130/80 and returned to its preoperative level 10 days after operation. The pulse rate was unaffected by the operation.

The angiographic studies were repeated 16 days after operation, 15 cc. of the iodopyracet solution being injected for the lateral and anteroposterior projections. A large plexus of dilated and tortuous veins was seen around the base of the skull and extending down the neck. The common facial vein, which, because of its high

site of origin from the internal jugular vein, had apparently not been ligated, showed pronounced varicosity. Fewer intracranial vessels were visualized than in the preanastomosis films or in those taken immediately after operation.

The child was discharged from the hospital three weeks after the fistula had been made. No physical or mental improvement was apparent.

COMMENT AND SUMMARY

Angiographic studies were made after the injection of a 35 per cent iodopyracet solution into the common carotid artery just proximal to the fistula. In cases 2 and 3, 12 and 15 cc., respectively, of the radiopaque medium was used for the postanastomotic arteriograms, rather than the 10 cc. used before anastomosis. Nevertheless, the number of cerebral arterial channels visualized was decreased, rather than increased.

The cerebral angiograms made before the fistula between the common carotid artery and the internal jugular vein was established showed no appreciable deviation from the anticipated normal. In the child with hydrocephalus *ex vacuo* the callosal branch of the anterior cerebral artery was elevated, in conformity with the dilated lateral ventricle. In the patients with small ventricles the location and caliber of the arteries and veins were normal.

After creation of the arteriovenous fistula the angiograms revealed a striking difference in the vascular pattern. The iodopyracet entered the right internal jugular vein and passed into the right transverse sinus, then across the midline to the left transverse sinus and the left internal jugular vein. Very little dye entered the intracranial carotid circulation. However, the patency of these arteries was demonstrated by the injection of iodopyracet into the cranial end of the fistula, revealing an essentially normal arterial pattern.

It seems likely that the route taken by the iodopyracet, which diffuses rapidly into the blood, is the same as that of the blood as it passes from the lowermost portion of the common carotid artery and traverses the carotid artery–jugular vein fistula. Hence the amount of blood entering the right cerebral hemisphere by way of the carotid artery would appear to be decreased. Most of the blood flowed into the jugular vein. In one case some of this blood from the right jugular vein entered the right transverse sinus and then flowed to the superior sagittal sinus and its tributaries. It is true that in this case the tributary venous system carrying arterial blood was a rich one. In this case, however, much of the arterial blood from the right transverse sinus flowed directly into the left transverse sinus and left the skull by way of the left jugular vein. In this way arterial blood by-passed the cerebral tissue. It is questionable whether the gain of arterial blood within the branches of the superior sagittal sinus in this case offset the loss resulting from the decreased amount of blood passing through the usual internal carotid pathway.

The superior sagittal sinus, which provides venous drainage for a large portion of the cerebral cortex, emptied into the right transverse sinus in our cases. This was seen in arteriograms made before the establishment of the arteriovenous fistula. After the anastomosis, however, the preferential flow of arterial blood from the right internal jugular vein and the transverse sinus appeared to be, for the most part, directly across to the left transverse sinus and the left internal jugular vein, rather than through the superior sagittal sinus.

In an attempt to explain the improvement reported by Beck, McKhann and Belnap in 20 to 30 per cent of their cases, several hypotheses have been examined.

Experimental observations in general have shown that an increased cerebral blood flow is accompanied with vasodilatation of the cerebral arteries.[2] In some instances, however, it seems that "the cerebral vasoconstriction is of a degree which is not overcome by the moderate elevation of the systemic arterial pressure." One cannot, then, draw inferences concerning the cerebral blood flow from the number of blood vessels seen in an angiogram. The fact that in the angiogram fewer small blood vessels in the brain are visible might indicate a greater cerebral blood flow provided that the systemic blood pressure had increased. But when, as in our cases, the systemic blood pressure does not increase, it is unlikely that the cerebral blood flow has increased.

Our cases present evidence that much of the arterial blood from the common carotid artery is diverted by the operation to the internal jugular vein. Most of this blood circulates through the right and then the left transverse sinus and leaves the skull by way of the left internal jugular vein. This arterial circuit through the venous system, by-passing to a large extent the superior sagittal sinus, results in loss of arterial blood to the brain. In our patients there was no accompanying increase in blood pressure. It is doubtful, therefore, whether a decrease of oxygen tension, an increase of carbon dioxide tension or an accumulation of metabolic products in the blood, such as might result from this shunting of arterial blood to the venous system, would increase the cerebral blood flow sufficiently to compensate for the lost arterial blood.

In this connection, the following conjecture presents itself: The improved functional activity reported after anastomosis of the common carotid artery and internal jugular vein may arise from the cerebral venous congestion caused by interruption of the jugular vein, slowing down the blood flow and thereby increasing greatly the normal consumption of oxygen by the cerebral neurons. The studies of Beck, McKhann and Belnap do not support this conjecture, however, for they indicate that cerebral blood flow after the establishment of the arteriovenous fistula is increased rather than decreased. The measure-

2. Wolff, H. G.: The Cerebral Circulation, Physiol. Rev. **16**:545-596, 1936.

ments of cerebral blood flow by Beck, McKhann and Belnap were made by means of a "rough quantitative test." Further studies of cerebral blood flow and of arteriovenous oxygen differences before and after operation are required.

We have considered a final hypothesis in attempting to explain the reported improvement in some cases after the Beck, McKhann and Belnap operation. This explanation involves an analogy with cases of involuntary movements, rigidity and psychoses. In such cases improved physical and mental activity sometimes follows cortical ablation or interruption of neural pathways. It is worth noting that the cerebral blood flow has been found to be reduced by 23 per cent after frontal lobotomy in man.[3] Possibly, after establishment of a carotid-jugular fistula improvement may result similarly when the cortical blood supply decreases. It is unlikely, however, that such improvement will be progressive unless better rehabilitation technics are used after operation than before.

Final evaluation of the clinical effect of this operation in our patients cannot be made at this time. Improvement was reported by the parents of one of our patients, but examination of the child failed to substantiate this report. The wish seemed to have fathered the thought, as so often happens in cases of this kind.

Our angiographic findings cast doubt on the effectiveness of this operation in increasing the arterial blood supply to the cerebral cortex. Moreover, we have recently had under our care a patient who illustrated one of the complications that may attend the operation. In this child, aged 4 years, proptosis of the right eye began progressively to develop (fig. 4 *A*) two weeks after the establishment, at another hospital, of an anastomosis of the right common carotid and the right internal jugular vein. Because of the advancing proptosis and the danger of corneal ulceration and loss of sight, we decided to repair the fistula. Before doing this, a cerebral angiogram was made in the anteroposterior position. The needle was placed beneath the site of anastomosis, and the angiogram revealed pronounced dilatation of the cerebral veins, particularly the right transverse sinus. A rich, tortuous anastomotic plexus was present around the foramen magnum, and dilated and tortuous veins were present over the cerebral hemispheres as well, being rather more pronounced on the right side (fig. 4 *C*). A small amount of iodopyracet solution entered the superior sagittal sinus. At operation the veins in the neck presented an unusual degree of dilatation and tortuosity, almost resembling a venous aneurysm (fig. 4 *B*). The internal jugular vein

3. Shenkin, H. A.; Woodford, R. B.; Freyhan, F. A., and Kety, S. S.: The Effects of Frontal Lobotomy on the Cerebral Blood Flow and Metabolism, A. Research Nerv. & Ment. Dis., Proc. (1947) **27**:823-831, 1948.

could be seen entering the skull as a dilated and elongated structure. None of the iodopyracet entered the arterial circulation.

Within a few hours after the anastomosis was disjoined and the opening in the carotid artery closed, the proptosis receded to a striking degree (fig. 4 *D*). After this operation the angiogram returned to normal (fig. 4 *E* and *F*).

The sequence of events leading to the development of the proptosis and its recession indicates that progressive dilatation of the arteriolized retrobulbar veins caused the proptosis and that collapse of these veins after interruption of the fistula was responsible for its recession. At

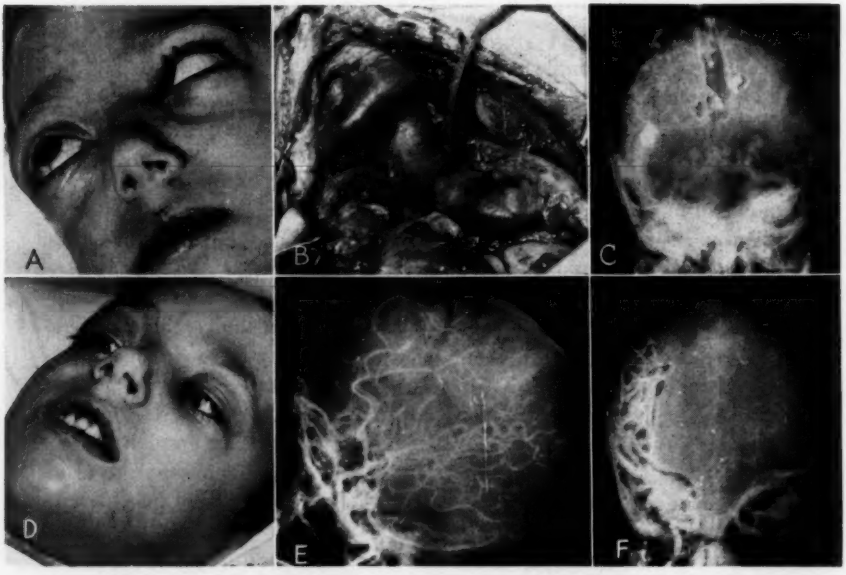

Fig. 4.—*A*, photograph of 4 year old child five months after the creation of an anastomosis of the common carotid artery and internal jugular vein at another hospital. Proptosis of the right eye is apparent.

B, site of the anastomosis exposed, revealing the tremendous dilatation of the internal jugular vein. The site of the anastomosis is indicated by arrow.

C, anteroposterior angiogram made before the anastomosis was corrected. The pronounced dilatation of the cerebral veins, as well as the venous plexus about the foramen magnum, is well shown. The contrast medium fills the right transverse sinus, and a small amount of dye is present in the superior sagittal sinus.

D, photograph of the face after interruption of the arteriovenous fistula. The proptosis has receded greatly.

E, postoperative angiogram after repair of the arteriovenous fistula. Iodopyracet injected into the common carotid artery visualizes a normal vascular tree.

F, anteroposterior angiogram, in the same series as *E*, showing a normal vascular tree.

operation the common facial vein [4] was found to have been greatly distended. The proptosis might have been due to arteriolization of the retrobulbar veins, either by way of the facial and angular veins or from the posterior cranial sinuses (right transverse, superior petrosal and cavernous).

Histologic study of the distended internal jugular vein and its ligated proximal stump showed extreme thinning of the wall of the arteriolized vein.

One wonders whether other complications due to progressive dilatation of these veins will occur in the course of time. Angiograms taken at successive intervals up to three months after creation of the fistula have shown definite expansion of intracranial and extracranial veins. In another of our cases (J. D.), moreover, proptosis began to develop

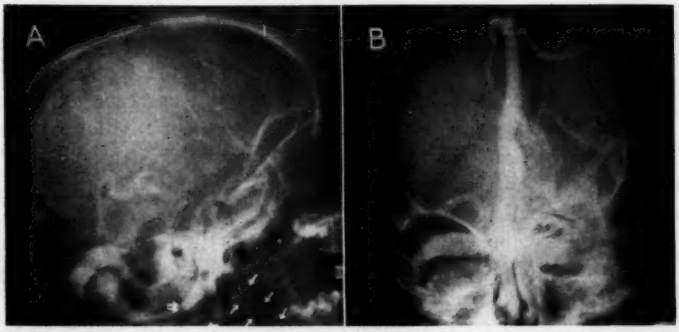

Fig. 5.—*A,* right lateral angiogram taken immediately after the injection of 12 cc. of 35 per cent iodopyracet solution into the common carotid artery 2 cm. proximal to the fistula. Most of the dye has entered the transverse sinuses, and some is seen in the superior sagittal sinus. The dye outlines several cerebral vascular channels. Both the right (double arrows) and the contralateral (single arrows) internal jugular vein are clearly seen.

B, anteroposterior angiogram taken one second after the completion of the injection of 12 cc. of 35 per cent iodopyracet solution. Both transverse and superior sagittal sinuses are densely opacified. Numerous tortuous and dilated cerebral veins, arising principally from the right side, are seen.

The subject of this arteriographic study was a 3 year old child in whom a fistula between the right common carotid artery and the internal jugular vein had been established one year previously.

three months after operation. Further complications may appear in these cases on the basis of dilatation of veins subjected to unaccustomed arterial pressures.

4. When this operation is performed, all extracranial veins should be ligated in order to minimize the drainage of arterial blood from the jugular vein before it enters the skull, as suggested by the originators of this operation. This cannot always be done, however, because some of the veins enter the jugular trunk close to the base of the skull and are inaccessible.

Consideration should be given also to the possible occurrence of late cardiac complications, well known in association with arteriovenous aneurysms, especially those situated close to the heart. In these cases cardiac hypertrophy and failure or bacterial endarteritis may not occur until after a considerable period has elapsed. Because of this danger, and because the intended clinical effect of anastomosis of the carotid artery and jugular vein remains *sub judice*, it seems advisable at present to limit further experience with this operation to the observation of those patients in whom the fistula has already been established.

CONCLUSIONS

Establishment of an arteriovenous fistula between the right common carotid artery and the internal jugular vein in three patients, according to the technic of Beck, McKhann and Belnap, did not increase the number of blood vessels visible in cerebral angiograms.

The chief effect of the operation was to divert the stream of arterial blood from the right common carotid artery to the internal jugular vein and thence to the right transverse sinus. In one case some blood from the right transverse sinus entered the superior sagittal sinus and its tributary cortical branches. The main vascular stream, however, continued from the right to the left transverse sinus and left the skull via the left internal jugular vein.

Proptosis, a complication of the operation, is the result of progressive dilatation of retrobulbar veins. Other veins carrying arterial blood also undergo progressive enlargement. One wonders, therefore, whether other cardiovascular complications may not occur in the course of time.

These studies provide no basis for optimism regarding the outcome of such operations for increasing the vascularization of the brain.

NOTE.—Since completion of this paper, we have had the opportunity of making an arteriographic examination on a 3 year old child in whom an anastomosis between the common carotid artery and the internal jugular vein had been performed one year previously by the originators of the operation. Arteriograms showed both transverse sinuses and the superior sagittal sinus with some of its large tributary cerebral veins, mostly on the right side. The number of cerebral blood vessels visualized was far below normal (fig. 5). Six weeks later this child was brought into the hospital in coma, resulting from subarachnoid hemorrhage. Recovery followed interruption of the fistula.

We reached the same conclusions from our angiographic studies on three other children, in whom either the external or the common carotid artery was anastomosed to the internal jugular vein on the right or the left side.

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FURTHER EXPERIENCES IN TREATMENT OF SEPTIC MENINGITIS WITH BACITRACIN

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DURING the past two years, 13 patients with purulent meningitis have been treated with bacitracin. The organisms and their incidence were as follows: Staphylococcus, six cases; Streptococcus, two cases; Pneumococcus, one case; mixed organisms, two cases, and an unidentified gram-positive coccus, two cases (table 1).

STAPHYLOCOCCIC MENINGITIS

Of the group of six patients with staphylococcic meningitis, five are reported on in a separate article.[1] All these 6 patients were treated with bacitracin by the intrathecal or the intraventricular route, or by both routes whenever such a method was indicated. This therapy was supplemented by the intramuscular injection of bacitracin and other antibiotics when that seemed advisable. In every instance the causal organism was found to be resistant to penicillin, which, in fact, had previously been used in excessive amounts both by subarachnoid and by intramuscular injections, with no avail. After bacitracin therapy five patients recovered and one died. The five cases of survival have been described in detail elsewhere[1] (table 1). The histories of the six patients are summarized.

CASE 1 (Bacitracin Series 2011).—G. L., a man aged 65, a patient of Dr. W. A. Altemeier, was admitted to the Cincinnati General Hospital on April 15, 1948 and discharged on July 22, 1948.

The patient was admitted to the hospital in a stuporous condition. Physical examination revealed a fracture of the base of the skull and a cerebral contusion. He was first treated with sulfadiazine but remained in a comatose state for 10 days. Culture of the cerebrospinal fluid revealed Staphylococcus pyogenes var. aureus. Penicillin was then added to the treatment by intramuscular injections,

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The bacitracin used was supplied by the Commercial Solvents Corporation, Terre Haute, Ind.

1. Teng, P., and Meleney, F. L.: Treatment of Staphylococcic Meningitis, with a Review of the Literature and with Particular Reference to the Results with Bacitracin: A Report of 5 Cases, Surgery **28**:516-533, 1950.

TABLE 1.—*Summary of Data in Thirteen Cases of Purulent Meningitis*

Type of Meningitis	Case No.	Age, Yr.	Sex	Treatment Before Bacitracin	Source of Infection	Disease Other Than Meningitis	Treatment with Bacitracin and Other Antibiotics	Result
Staphylococcus	1*	65	M	Sulfadiazine; penicillin	Fracture of base of skull	Cerebral contusion	Bacitracin: intramuscular, intraventricular	Cure
	2*	50	M	Sulfonamides; penicillin; streptomycin	Infected craniotomy wound	Brain tumor	Bacitracin: local, intrathecal, intramuscular	Cure
	3*	62	F	Penicillin	Infected craniotomy wound	.....	Bacitracin: intramuscular, intracranial	Cure
	4*	6 wk.	F	Penicillin; sulfadiazine; aureomycin; streptomycin	Septicemia	Multiple abscesses	Bacitracin: intramuscular, intrathecal Aureomycin: oral Penicillin: intramuscular	Cure
	5*	27	M	Sulfadiazine; penicillin	Septicemia	Carbuncle of leg	Bacitracin: intramuscular, intrathecal, intraventricular Penicillin: intramuscular	Cure
	6	16	F	Penicillin	Infected craniotomy wound	Pineal tumor	Bacitracin: intramuscular, intrathecal, intraventricular Penicillin: intramuscular	Death
Streptococcus	7	43	M	Penicillin; streptomycin; aureomycin; sulfadiazine	Middle ear	Brain abscess	Bacitracin: intramuscular, intraventricular, intracerebral, intrathecal	Cure
	8	54	M	.....	Middle ear	Brain abscess; coronary occlusion; bronchopneumonia; diabetes mellitis	Bacitracin: intramuscular, intrathecal Streptomycin: intramuscular, intrathecal Penicillin: intramuscular, intrathecal	Death
Pneumococcus	9	6 mo.	M	Penicillin	Middle ear	Subdural hematoma, bilateral; left side infected	Bacitracin: intramuscular, intrathecal, into each hematoma Penicillin: intramuscular Sulfadiazine: oral	Cure
Mixed type, Staphylococcus and Ps. aeruginosa	10	63	M	Penicillin; streptomycin; aureomycin; chloromycetin	Infected craniotomy wound	Thrombosis and extensive infarction of middle cerebral artery; diabetes mellitus	Bacitracin: intramuscular, intrathecal Penicillin: intramuscular Aureomycin: oral Streptomycin: intramuscular	Death
Mixed type, Staphylococcus and Streptococcus	11	15	M	Penicillin; sulfonamides	Ethmoid and sphenoid sinus	Brain abscesses; purulent encephalitis	Bacitracin: intramuscular, intrathecal, intraventricular Penicillin: intramuscular	Death
Gram-positive cocci, unidentified	12	76	M	.....	Unknown	.....	Bacitracin and penicillin: intramuscular, intrathecal Sulfadiazine: oral	Cure
	13	46	F	.....	Septicemia	Brain tumor; diabetes mellitus	Bacitracin: intramuscular, intrathecal Penicillin: intramuscular	Cure

* Described in detail in a separate article in Surgery.[1]

and 25,000 units was instilled into each lateral ventricle by ventricular taps daily for four days. In spite of the combined therapy, the illness continued to run a febrile course with cerebrospinal fluid cultures yielding the organism. The Staphylococcus was found to be resistant to penicillin but susceptible to bacitracin. Therefore, treatment with all other agents was stopped, and intraventricular injections of bacitracin were given, in doses of 5,000 units dissolved in 4 cc. of cerebrospinal fluid daily for six days, supplemented with 25,000 units injected intramuscularly every four hours for eight days. Five days after the initiation of bacitracin therapy, the patient slowly recovered consciousness. Repeated cultures of the cerebrospinal fluid had yielded no pathogens since the start of bacitracin therapy. The patient made a good recovery.

CASE 2 (Bacitracin Series 1107).—F. B., a man aged 50, a patient of Dr. Wilder Penfield, was admitted to the Montreal Neurological Institute on Dec. 20, 1948 and discharged on March 5, 1949.

Seven days after a craniotomy on the right side, the wound gave evidence of infection. The cerebrospinal fluid showed 1,500 white blood cells per cubic millimeter. The flap was then removed. The patient was treated with systemic administration of penicillin and sulfadiazine-sulfamerazine-sulfamethazine mixture (triple sulfonamides) for 19 days, without obvious effect. Five days later streptomycin therapy was started and continued for 15 days. In addition to the systemic treatment, the sulfonamides, streptomycin and penicillin were instilled locally into the wound under the scalp. On the twenty-seventh day the patient's neck became increasingly rigid. The wound was explored, and a subdural abscess was found and drained. Cultures of the contents of the abscess and of the lumbar cerebrospinal fluid yielded a coagulase-positive Staphylococcus, which was resistant to 100 units of penicillin and required 32 units of streptomycin for inhibition but was sensitive to 0.85 unit of bacitracin. Bacitracin was therefore administered by local instillation into the abscess cavity in a dose of 10,000 units in 10 cc. of isotonic sodium chloride solution three times a day. This amount was reduced to 5,000 units after the eighth day and the dose continued for 16 days. Bacitracin was also given by the intraspinal route, in doses of 5,000 units in 5 cc. of isotonic sodium chloride solution, on the first, second, fourth and seventh days. Ten thousand units was injected intramuscularly every six hours for 10 days. The patient made an uneventful recovery.

CASE 3 (Bacitracin Series 1100).—S. T., a woman aged 62, a patient of Dr. F. A. Echlin, was admitted to the Lenox Hill Hospital, New York, on Sept. 10, 1948 and discharged on Feb. 17, 1949.

Seventeen days after a cortical ablation of the right frontal lobe, the wound was found to be infected and was explored. A large quantity of purulent fluid was evacuated. Culture of the fluid showed Staphylococcus pyogenes var. albus, which completely resisted penicillin but was sensitive to bacitracin. Bacitracin was therefore instilled into the wound every three hours through a catheter in a dose of 10,000 units in 10 cc. of isotonic sodium chloride solution. An intramuscular injection of 10,000 units of bacitracin was given every six hours for 10 days. Ten days after the beginning of bacitracin therapy the culture of material from the wound became sterile and remained so. The local instillation of bacitracin was carried on for 32 days. The wound gradually healed, and the patient recovered.

CASE 4 (Bacitracin Series 1080).—M. B., a female infant aged 6 weeks, a patient of Dr. Hattie Alexander, was admitted to the Babies Hospital, New York, on Jan. 15, 1949 and discharged on Feb. 13, 1949.

This 6 week old, premature baby had a huge abscess on the right side of the face, evidently arising from pansinusitis. She had been treated systemically with penicillin and streptomycin for six days. A lumbar puncture performed at that time showed that the cerebrospinal fluid was turbid, with 7,300 neutrophils. Culture of the cerebrospinal fluid showed a Staph. pyogenes var. aureus. Penicillin, 1,500 units, was therefore injected intraspinally. The systemic doses of penicillin were raised to 200,000 units every three hours, and administration of sodium sulfadiazine, 0.06 Gm. every six hours, was started. On the following day the baby became lethargic. Administration of aureomycin was started by mouth and streptomycin intraspinally. Despite this treatment, cultures of the blood and the cerebrospinal fluid yielded the organism on the tenth, eleventh and twelfth days. On the next day treatment with bacitracin was started, in a dose of 400 units per kilogram of body weight every six hours injected intramuscularly and 500 units in 3 cc. of isotonic sodium chloride solution given twice a day by the intraspinal route. On the third day of bacitracin therapy the child seemed more responsive, and her condition thereafter steadily improved. On the fourth day of bacitracin treatment the cultures of the cerebrospinal fluid and blood were sterile and remained so. The intraspinal injection of bacitracin was stopped four days later, and the intramuscular treatment was continued for another week. The baby made a complete recovery.

Case 5 (Bacitracin Series 1129).—F. M., a man aged 27, a patient of Dr. C. G. Craddock Jr., was admitted to the University of Virginia Hospital on Aug. 17, 1949 and discharged on Sept. 16, 1949.

Following the incision of a carbuncle of the leg, the patient showed signs of meningitis. Lumbar puncture revealed cloudy cerebrospinal fluid, containing 32,000 white blood cells, most of which were neutrophils. Culture of the cerebrospinal fluid showed a hemolytic Staph. pyogenes var. aureus. The patient was treated with penicillin, 200,000 units every three hours, and sulfadiazine, 1 Gm. every four hours for three days. In spite of this treatment he became comatose. Penicillin, 25,000 units, was instilled into the left lateral ventricle after a spinal block was disclosed by manometric test. On the following day the patient was considerably worse, being in a stuporous condition and unable to respond. It was then decided to shift to the use of bacitracin. A dose of 9,800 units of bacitracin was injected into the left lateral ventricle and the same amount into the lumbar subarachnoid space. This treatment was supplemented with intramuscular injections of bacitracin. On the second day of bacitracin therapy the cultures of the ventricular and spinal fluid were sterile. On the third day of this treatment the patient came out of his coma. Thereafter he made steady improvement and recovered completely.

Case 6 (Bacitracin Series 1121).—I. D., a girl aged 16, a patient of Dr. Benno Schlesinger, was admitted to the Mount Sinai Hospital on Feb. 16, 1949 and died on June 12, 1949.

An exploratory craniotomy performed on March 3, 1949 disclosed a tumor in the pineal region, which was not removed. Because of complete block of the ventricular system at the aqueduct, Torkildsen's tube was placed to short-circuit the cerebrospinal fluid from the posterior horn of the right lateral ventricle to the cisterna magna. Twenty-six days later her symptoms recurred and the tube was found clogged. Two days later the same operation was repeated and the tube was replaced. Twelve days after the second operation the tube was revised for the third time because it was blocked at its lower end. Despite the large preventive daily doses of penicillin, her temperature reached 103 F. on the fifth day after the third operation. The occipitocervical wound showed frank discharge of pus, culture of which revealed Staph. pyogenes var. aureus. The wound was laid open and irrigated with penicillin solution, 1,000 units per cubic centimeter. Two

days later, her neck became stiff, and the cerebrospinal fluid flowed out through the wound. Lumbar puncture revealed cloudy fluid, containing 11,680 white blood cells, with 98 per cent neutrophils and a total protein of 500 mg. per 100 cc. Culture of the cerebrospinal fluid yielded the same pathogen as that from the wound, and the organism was found to be resistant to both penicillin and streptomycin. She was then treated with bacitracin, in a dosage of 5,000 units once daily by intraspinal injection and 10,000 units every six hours by the intramuscular route. Through a catheter of small caliber inserted into the wound, 10 cc. of a solution of bacitracin containing 500 units per cubic centimeter was used for irrigation. On the day following this treatment, her neck became soft, and her severe headache completely disappeared. Eleven days later the wound healed completely, with the Torkildsen tube still buried in the wound. The cerebrospinal fluid was grossly clear. Repeated culture showed no growth. However, the fluid still contained 510 leukocytes and 130 mg. of total protein per 100 cc. Two days later the tube was removed through a small incision made in the occipital region. This procedure was followed by recrudescence of the meningitis. At this time, in addition to the intraspinal and intramuscular therapy, 10,000 units of bacitracin was given once a day by intraventricular injection. In spite of the clearing of the ventricular fluid, the patient was lethargic, owing to the increased intracranial pressure resulting from the block of the ventricular system. Therefore, as a last resort, a ventriculostomy was performed. At the operation the exposed portion of the base of the brain showed no sign of meningitis. At the end of the operation, 10,000 units of bacitracin in 10 cc. of isotonic sodium chloride solution was injected into the cranial cavity. After operation the patient continued to receive bacitracin and penicillin intramuscularly, but the intraspinal and intraventricular injections were stopped. The wound healed five days later. At this time, she was alert, her temperature was normal and she had neither vomiting nor headache. However, one week later the signs and symptoms of increased intracranial pressure reappeared, as a result of the closure of the ventriculostomy opening. An indwelling catheter, therefore, was placed in the right lateral ventricle through its anterior horn for continuous underwater drainage. Through the catheter, 5,000 units of bacitracin was injected daily into the ventricle. In spite of this treatment, she continuously had a septic temperature. Her general condition gradually became worse, and her level of consciousness was lowered progressively. Ten days later the intraventricular therapy was stopped. A ventriculogram demonstrated that the mass previously outlined had increased three times in size. One week later she was deeply lethargic. She died on June 12, 1949, of massive intraventricular bleeding. Autopsy revealed evidence of infection of the ventricles, the base of the brain with its coverings and the spinal meninges.

In this case, surgical procedures to short-circuit the cerebrospinal fluid circulation, which was blocked at the aqueduct and the third ventricle by a tumor in the pineal region, had repeatedly failed. In spite of the large preventive doses of penicillin which were given after operation, infection occurred as a result of repeated operations through the same wound and within brief intervals. The organism was found to be resistant to penicillin but sensitive to bacitracin. Bacitracin demonstrated its effectiveness in the primary control of the infection, but was not effectual because the stagnation of the cerebrospinal fluid could not be overcome.

STREPTOCOCCIC MENINGITIS

Two patients with streptococcic meningitis were treated with bacitracin. One recovered.

CASE 7 (Bacitracin Series 1084).—P. R., a man aged 43, a patient of Dr. Fritz J. Cramer, was admitted to the Neurological Institute, New York, on Jan. 2, 1949 and discharged April 2, 1949.

Six weeks before admission the patient had had one tooth extracted from each side of his lower jaw. On the third day after the extraction he showed signs of infection, and he was given penicillin in doses varying from 300,000 to 1,000,000 units daily. However, despite several incisions for drainage and the penicillin therapy, the infection continued. Two and one-half weeks before his admission his right ear began to drain, and this continued up to the time of admission. Four days before his admission a peritonsillar abscess was drained, and several sequestrums were removed from the jaw. Seven hours prior to his admission, pain developed in the neck and shoulders, with rising temperature, nausea, vomiting and general malaise.

On admission the patient was acutely ill. His temperature was 103 F.; the pulse rate was 124, and the respiration rate 44, per minute. The white blood cells numbered 22,900, with 93 per cent segmented granulocytes. A diagnosis of meningitis was made, and lumbar puncture revealed a cloudy fluid. The cell count was 17,280, with cells almost entirely segmented forms. Gram-positive cocci were found in the fluid. Penicillin, in a dose of 30,000 units in 5 cc. of isotonic sodium chloride solution, was introduced slowly into the lumbar subarachnoid space. This treatment was supplemented with systemic administration of the drug, in doses of 200,000 units every three hours, and of streptomycin, 1 Gm. every four hours. A roentgenogram revealed apparent involvement of the right mastoid, a lesion of the mandible at the site of extraction of the tooth and an area of consolidation of the left upper lung field. A mastoidectomy was immediately performed. Only sclerotic cells were observed in the mastoid, but pus welled up from the tympanum of the middle ear. The plate above the tympanum appeared to be missing entirely. This pointed to the portal of entry of the infecting organisms into the subarachnoid space. Cultures of the pus obtained at this operation showed no growth. The wound was left open, and the cavity was packed.

On the following day, the intramuscular dose of penicillin was increased to 500,000 units every three hours; streptomycin was given instead of dihydrostreptomycin, 1 Gm. every six hours, and at the same time the patient was given sulfadiazine, 2 Gm. every six hours. Lumbar puncture was performed both morning and evening. The fluid withdrawn was cloudy, and penicillin, in a dose of 15,000 units in 10 cc. of isotonic sodium chloride solution, was instilled. On the morning of the third day of hospitalization, the lumbar puncture was repeated, and a similar dose was injected. In the evening the intrathecal dose was increased to 30,000 units. The dressing on the ear was changed on the third day, the packing removed, a catheter placed for local instillation of medicaments and 5 cc. of sulfamylon® (4-amino-2-methylbenzenesulfonamide) was instilled into the cavity through the catheter. The patient's temperature fell during the second day but then started to rise again, reaching 102 F. on the third day and 104.2 F. on the fourth day. His pulse rate rose to 148, and his respiration rate to 42, per minute. The dose of penicillin was increased to 1,000,000 units every three hours, and 100 mg. of aureomycin was given.

On the fifth day a trephine opening was made in the right temporal region. With an exploring needle an abscess was found in the right temporal lobe of

the brain, and greenish yellow pus was obtained. Culture of the pus revealed Streptococcus viridans. A no. 8 French catheter was inserted into the abscess cavity, which was irrigated with penicillin solution containing 1,000 units per cubic centimeter. On the day after operation the patient's temperature reached 104.2 F. and then fell to a lower level. Meanwhile a lumbar puncture was done twice a day, and penicillin was injected intraspinally in doses ranging from 10,000 to 30,000 units at each session. The spinal fluid cleared considerably, and the number of cells fell from 17,280, on the first tap, to 62 per cubic millimeter, but the cell count then rose again, and the spinal fluid became yellowish and finally turbid. On the day after the operation the systemic dose of penicillin was increased to 2,000,000 units every three hours, and the following day the temperature became normal. However, it gradually rose again to higher levels and ranged from 100 and 101.6 F. until the twelfth postoperative day.

On the thirteenth day he was again taken to the operating room, and bilateral frontal burr holes were made. Attempts to enter the right ventricle were unsuccessful; but the left was easily entered, and purulent fluid was withdrawn, 20 cc. being removed and replaced with an equal amount of air. A ventriculogram demonstrated that the abscess communicated with the ventricular system; the abscess was then excised. Each day a ventricular tap revealed cloudy fluid, which was replaced with 20,000 units of penicillin in an equal amount of isotonic sodium chloride solution. Although the temperature fell to a lower level for the first four days, it rose again on the fifth day, and the patient became comatose, with pronounced spastic hemiparesis. It was thought that the patient probably had other, undrained abscesses, and the outlook seemed extremely unfavorable.

On the twenty-fourth day of hospitalization it was decided to try bacitracin. Ten thousand units was given every six hours intramuscularly and 3,000 units in 10 cc. of isotonic sodium chloride solution was instilled into the left ventricle twice a day. On the twenty-sixth day, 5,000 units in 3 cc. of isotonic sodium chloride solution was injected intraspinally after lumbar puncture morning and evening. This treatment was continued daily; the temperature gradually came down, and on the third day following the initiation of bacitracin treatment the patient began to come out of his coma. He became alert and more responsive. On the thirty-fourth day of hospitalization, and after nine days of intraspinal treatment, instillation of bacitracin by this route was reduced to once a day. Six days later it was stopped altogether. On the fifteenth day of intraventricular injections the instillations were made once a day and eight days later were discontinued. The patient recovered, except for residual weakness of his left arm. He was alert mentally, but his gait was unsteady. Two months after discharge he returned to the Medical Center for removal of a kidney stone. This hospital experience was without incident.

During the course of bacitracin therapy, use of penicillin was inadvertently continued by intramuscular injections during the first sixteen days but was then stopped, without any apparent change, either favorable or unfavorable, in the patient's condition. The blood urea nitrogen one week before the beginning of bacitracin therapy was 17 mg. and the nonprotein nitrogen on the day after starting use of the drug was 35 mg. per 100 cc., but during the course of treatment after 23 days the nonprotein nitrogen had fallen to 27 mg. per 100 cc.

A strange feature of this case is that a positive culture of the cerebrospinal fluid was obtained only once, when the brain abscess was first entered and the pus yielded a nonhemolytic Streptococcus. All other cultures showed no growth on mediums designed for ordinary bacteria, fungi and tubercle bacilli. It may be that the causative organism was a

slow-growing anaerobic Streptococcus. Apparently, the treatment which the patient received rendered it difficult for the organism to grow. However, doses as large as 16,000,000 units of penicillin a day failed to control the infection, whereas bacitracin within a few days brought the patient out of his coma and carried him through to an apparent recovery, except that the damage done to the brain tissues by the abscess may have left him with certain residual symptoms.

CASE 8 (Bacitracin Series 1124).—M. L., a man aged 54, a patient of Dr. Abraham Kaplan, was admitted to the Mount Sinai Hospital on May 21, 1949 and died on June 2, 1949.

The patient had been a known diabetic for 10 years. Two weeks before admission, he had sudden onset of pain in the left ear. The next morning he bought some medicine from a drugstore and instilled it into his left ear. One week later he began to have left frontal headache and difficulty in remembering names of people and objects.

Examination revealed weakness of the right side of the face of central type, and his tongue deviated to the right side. There were definite mental symptoms of organic type and anosmia. Tenderness was elicited over the left frontal region, and a partially healed perforation of the drum membrane of the left ear was found. His temperature was normal. An electroencephalogram showed a focal lesion in the left temporal lobe. Laboratory findings were normal except for a blood sugar of 240 mg. per 100 cc. and a 4 plus reaction for sugar in the urine.

On the third day after admission the patient became very lethargic. A ventriculogram, performed on the fifth day, revealed a shift of the ventricular system to the right. Exploration through a bone flap in the left temporoparietal region failed to disclose any lesion in the temporal lobe. An exploring needle was passed in several directions without encountering any tumor or abscess. After operation, the patient was given large doses of penicillin. On the next day he had nuchal rigidity and was deeply stuporous. Lumbar puncture yielded cloudy cerebrospinal fluid, which contained 32,000 white blood cells and 95 mg. of total protein per 100 cc. Smears showed gram-positive cocci, but, surprisingly, cultures yielded no growth. After removal of the cerebrospinal fluid, 10,000 units of bacitracin in 15 cc. of isotonic sodium chloride was instilled into the lumbar subarachnoid space. Systemically, he was given procaine penicillin G, 600,000 units twice a day, and bacitracin, 10,000 units every four hours. From the third day after operation the intraspinal injection of bacitracin was given twice a day. However, the patient remained comatose, and the cerebrospinal fluid showed no signs of improvement. In spite of the large doses of insulin, the urine continuously showed a 4 plus reaction for sugar and acetone. In addition to the bacitracin therapy, he was given 10,000 units of penicillin and 50 mg. of streptomycin by the intraspinal route twice a day. On the fourth day of this combined therapy, extensive bronchopneumonia and cardiac fibrillation developed, and he died.

Autopsy revealed a noncapsulated and ruptured brain abscess in the left temporal lobe; meningitis; extensive bronchopneumonia, involving all lobes of the lungs; coronary arteriosclerosis with severe insufficiency and recanalization of the thrombus, and cardiac dilatation. Culture of the content of the brain abscess and of the lung yielded a pure culture of Streptococcus hemolyticus.

Despite the use of all available antibiotics that could be given by intraspinal and intramuscular injections, the patient's life could not be

saved. The entry of infection was obviously from the left middle ear. The abscess gave symptoms and signs of a brain tumor. Eventually, at the operation, it was ruptured by probing punctures, and the spreading of the infection resulted in meningitis. The uncontrolled diabetes further complicated the situation. In spite of the extensive antibiotic therapy, widespread bronchopneumonia developed and the patient died with cardiac insufficiency.

PNEUMOCOCCIC MENINGITIS

In this group only one patient was treated with bacitracin, with complete recovery. The meningitis followed the formation of bilateral subdural hematomas, one of which became infected.

CASE 9 (Bacitracin Series 1156).—J. R., a male infant aged 6 months a patient of Dr. Benno Schlesinger, was admitted to the Mount Sinai Hospital on Aug. 9, 1949 and discharged on Sept. 27, 1949.

Three weeks prior to admission the patient fell from a sofa and landed on his head. One day before admission he had sudden onset of fever, with a temperature of 105 F.

Physical examination on admission disclosed a full anterior fontanel, which measured 2 by 2 cm. The circumference of his head was 45 cm. He was very lethargic, but the neurological status was normal. Laboratory studies showed a blood cell count of 13,800, with 83 per cent segmented granulocytes, and a clear cerebrospinal fluid, containing 50 mg. of sugar, 573 mg. of chlorides and a total protein of 37 mg., per 100 cc., but no cells.

On the following day, his temperature dropped to 101.4 F., and he was more active and alert than he had been on admission. There was a mucopurulent discharge from his nostrils. A throat culture yielded Pneumococcus type 18 and Staph. pyogenes var. albus. In the afternoon his body temperature rose to 103.4 F., and there developed muscular twitchings, which were followed by generalized clonic convulsions. A puncture through the left lateral angle of the anterior fontanel yielded cloudy, xanthochromic fluid (from the left parietal region). This fluid contained 420 mg. of total protein per 100 cc. and 2,250 leukocytes, with a differential count of 85 per cent segmented granulocytes. From the opposite angle of the fontanel frankly bloody fluid was withdrawn. The cerebrospinal fluid obtained by lumbar puncture was turbid, containing 810 white blood cells, all of which were segmented granulocytes, and 50 mg. of sugar, 679 mg. of chlorides and 172 mg. of total protein, per 100 cc. Pneumococcus type 18 was isolated from the cultures of the cerebrospinal fluid and from the contents of the left subdural hematoma. The organism was sensitive to both penicillin and bacitracin.

Immediately after the removal of the cerebrospinal fluid by lumbar puncture, 10,000 units of penicillin in 10 cc. of isotonic sodium chloride solution was instilled into the subarachnoid space. After the intraspinal injection of penicillin the patient continued to have muscular twitchings with episodes of generalized convulsions for five hours. On the next day bacitracin, instead of penicillin, was injected intraspinally, using 1,000 units in 4 cc. of isotonic sodium chloride solution. Systemically, in addition to 300,000 units of procaine penicillin G twice a day, he was given 500 units of bacitracin every six hours by the intramuscular route. After daily aspiration through the anterior fontanel, 1,000 units of bacitracin was instilled into each subdural hematoma.

On the second day of bacitracin therapy, the patient was fully alert, cried aloud and took feedings voraciously. Cultures of the cerebrospinal fluid and of the fluid from both hematomas were sterile and thereafter remained so. By this time the tympanic membrane on each side was found to be full and red. Both were incised, and mucoid secretion was evacuated. Culture yielded the same organism as that in the cerebrospinal fluid. The cerebrospinal fluid on this day was clear and contained 115 cells per cubic millimeter.

On the fifth day of treatment, the cerebrospinal fluid was crystal clear, and the fluid from the hematomas was clear but xanthochromic. The intraspinal and intramuscular injections of bacitracin were stopped. Instillation of the drug into the hematomas was continued until the tenth day, at which time the subdural hematoma on the right side was evacuated by a bone flap operation. At the end of the operation, 2,000 units of bacitracin was instilled into the subdural space, and the same amount was placed under the scalp. The subdural space was drained for two days, and 1,000 units of bacitracin was injected daily through the drain until it was removed. After operation, the patient was again given bacitracin by intramuscular injection, in a dose of 500 units every six hours for six days. The wound healed by primary union on the sixth postoperative day. However, the brain failed to expand, and the hematoma was again found filled with xanthochromic fluid. Every day 50 to 100 cc. of fluid was removed by fontanel puncture, and 1,000 units of bacitracin was instilled into the hematoma once every other day.

On the fifteenth day after the patient's admission the subdural hematoma on the left side was found dry on aspiration. Eight days later no fluid could be found on the right side. The temperature and cerebrospinal fluid were normal. A pneumoencephalogram performed in the fifth week revealed bilateral dilatation of the lateral ventricles. There was no shift of the ventricular system. One week later a burr hole was made in the left parietal area. The dura, arachnoid and cortical surface were all normal, and no constricting membrane of the hematoma was found.

During the course of bacitracin therapy, the urine occasionally showed a trace of albumin; and in two examinations a few granular casts were noted, but there were no other signs of renal irritation. The patient was discharged after seven weeks, in good condition, having gained 2½ pounds (1,134 Gm.) during his stay in the hospital. Three months later he was seen at the follow-up clinic, a normal-looking baby with no neurological abnormalities.

This case illustrates the effectiveness of bacitracin therapy in pneumococcic infections of the meninges. The local instillation of bacitracin into the cerebrospinal space and the subdural hematomas rapidly cleared up the infection and exerted no ill effect on the tissues of the central nervous system. Convulsions, which developed before and after the intraspinal injection of penicillin, never appeared during the course of intraspinal therapy with bacitracin.

MENINGITIS OF MIXED INFECTION

Two patients in this group were treated with bacitracin after other antibiotic therapy had failed. The meninges and the brain tissue of one patient were found to be infected with Staph. pyogenes var. albus and a hemolytic Streptococcus. The culture of the brain tissue of the other yielded a Pseudomonas aeruginosa (Bacillus pyocyaneus) and Staph. pyogenes var. aureus. Both patients died.

CASE 10 (Bacitracin Series 1125).—L. W., a man aged 63, a patient of Dr. Leo Davidoff, was admitted to the Beth Israel Hospital, New York, on April 13, 1949 and died May 28, 1949.

The patient, a known diabetic for 15 years, was admitted because of complete hemiplegia and hemianesthesia resulting from thrombosis of the right middle cerebral artery. The course of illness was complicated by an infection of the urinary tract, which was treated with penicillin, streptomycin, aureomycin and chloramphenicol (chloromycetin®). On the twenty-fifth day after his admission, there developed signs of an expanding lesion in the right cerebral hemisphere. After an air study, a craniotomy was done, and an extensive infarction of the right hemisphere was found. The postoperative course was marked by a septic fever, and the intracranial pressure was found further increased. Lumbar puncture on the tenth postoperative day showed cloudy cerebrospinal fluid, containing 3,200 white blood cells, all of which were segmented granulocytes, but the culture showed no growth. On the next day, the wound was reexplored, and necrotic brain tissue was partially removed. Culture of the brain tissue revealed Ps. aeruginosa and Staph. pyogenes var. ar. aureus. Two days later the treatment was shifted to bacitracin, 2,500 units by intracerebral injection and 5,000 units by intramuscular injection. The patient showed no improvement and died on the third day of bacitracin therapy.

In infections caused by Ps. aeruginosa bacitracin is ineffective. Moreover, the thrombosis of the middle cerebral artery and the extensive infarction of the cerebral hemisphere in this case provided a fertile soil for the growth of the organism. In such a condition all presently available treatment is of no avail.

CASE 11 (Bacitracin Series 6002).—W. B., a youth aged 15, a patient of Dr. Francis G. Grant, was admitted to the Hospital of the University of Pennsylvania on Oct. 25, 1948 and died on Jan. 28, 1949.

After ethmoidosphenoiditis, there developed multiple abscesses of the brain, which were drained three times in seven months. On the day of the patient's last admission another abscess was drained through a brain cannula. On the sixth and seventh days, respectively, 200,000 units of penicillin was injected into the abscess cavity. On the twelfth day an operation was performed to evacuate the abscess. From the day before this operation to the twelfth day after it, the patient was treated with penicillin, sulfadiazine and sulfamerazine.

On the seventeenth day after his admission, and five days after the abscess was last drained, the patient showed clinical signs of meningitis. The cerebrospinal fluid contained 7,000 cells, all segmented granulocytes. Culture of the ventricular and spinal fluids yielded a nonhemolytic Streptococcus and a hemolytic Staph. pyogenes var. albus. Both organisms were resistant to penicillin and streptomycin but susceptible to bacitracin. On the eighth day of the meningitis, bacitracin therapy was started with intraventricular injection of 12,000 units in 1.5 cc. of isotonic sodium chloride solution daily for nine days and 15,000 units every four hours by the intramuscular route for 15 days. On the fifth day of bacitracin treatment, the cultures of ventricular and spinal fluid were sterile and remained so. Three days later the cell count of the spinal fluid was 120 per cubic millimeter. However, the clinical course did not improve, and the patient's condition became gradually and steadily worse. The patient died two months after bacitracin therapy had been stopped. During this two month period, penicillin, sulfadiazine and sulfamerazine had again been administered, without avail.

Autopsy revealed purulent encephalitis and incomplete walling off of a brain abscess.

This case illustrates the temporary control of infection in the cerebrospinal fluid and meninges, but the patient finally succumbed to extensive purulent encephalitis, extending outward from an undiscovered abscess. Sensitivity tests showed that the organisms were sensitive only to bacitracin.

MENINGITIS DUE TO AN UNIDENTIFIED GRAM-POSITIVE COCCUS

CASE 12 (Bacitracin Series 1123).—M. K., a man aged 76, a patient of Dr. Israel S. Wechsler, was admitted to the Mount Sinai Hospital on May 31, 1949 and discharged on June 17, 1949.

One week before admission the patient suddenly fell ill with a severe headache and a temperature of 105 F. Two days before he fell sick, he had "caught cold." On the evening of the day of admission he exhibited a generalized convulsion, which lasted about half a minute. After the seizure he vomited repeatedly.

Examination revealed that the patient was severely dehydrated. His tongue was thickly coated, and his skin was dry. He was semistuporous and restless. He could neither answer nor understand simple questions or commands. His speech was thick. There was a coarse tremor of the left hand and arm. Deep reflexes of the lower extremities were all depressed. His neck was extremely rigid. The Kernig and Bruzinski signs were elicited. He was incontinent of urine. The urine gave a 1 plus reaction for albumin. The white blood cell count was 23,000, with 94 per cent neutrophils.

A lumbar puncture performed immediately on his admission yielded cloudy cerebrospinal fluid with an initial pressure of 260 mm., 182 mg. of total protein, per 100 cc. and 4,200 cells, all of which were segmented granulocytes. Direct smears showed gram-positive cocci, but repeated cultures gave no growth. A blood culture also yielded no growth. After 20 cc. of the cerebrospinal fluid had been removed, 10,000 units of bacitracin and 5,000 units of penicillin in 10 cc. of isotonic sodium chloride solution were instilled into the lumbar subarachnoid space. Systemically, the patient was given both antibiotics by the intramuscular route, 10,000 units of bacitracin in 1 cc. of 1 per cent procaine hydrochloride in isotonic sodium chloride solution every six hours and 300,000 units of procaine penicillin G once daily. In addition, he was given sulfadiazine, 1 Gm. every four hours for three days.

On the next day, the intraspinal injection of penicillin was increased to 10,000 units, while the dose of bacitracin was the same as before. The cerebrospinal fluid on this day was still cloudy and contained 8,000 cells and 135 mg. of total protein per 100 cc. The temperature dropped from 105 to 102 F.

On the third day, the intrathecal penicillin therapy was discontinued. Bacitracin alone was given by the intraspinal route. The systemic dose of penicillin was doubled. In the afternoon of this day the temperature became normal and remained normal thereafter. The cerebrospinal fluid was clearing. The patient was alert and answering questions well.

On the fourth day he was given only 5,000 units of bacitracin by intraspinal injection, and use of the drug was stopped on the next day. He was up and around on the sixth day. His headache had completely disappeared, the tremor of the hand had ceased and the incontinence of urine had cleared up. The cerebrospinal fluid

was crystal clear and contained 150 cells per cubic millimeter and 66 mg. of protein per 100 cc. All treatment was discontinued on the sixth day, and he was discharged from the hospital twelve days later, in good condition. The portal of entry of the infection remained unknown.

The causative organism was probably an anaerobic Streptococcus or Staphylococcus. A combination of bacitracin and penicillin therapy saved the life of the patient, a man of 76 years, the oldest patient with meningitis recorded as having survived.[2] Although the organism was not cultured from the cerebrospinal fluid, there was little doubt of the presence of meningitis in this case. The mental status, the tremor of the arm and hand, the incontinence of urine, convulsions and the cerebrospinal fluid findings, all spoke against the aseptic meningitis.

Case 13 (Bacitracin Series 1157).—R. R., a woman aged 46, a patient of Dr. Israel S. Wechsler, was admitted to the Mount Sinai Hospital on Sept. 13, 1949 and discharged on Dec. 16, 1949.

This was the third admission of the patient, who was diabetic. Eight years before she had an abscess of the upper lobe of the right lung, which was drained and healed. One year before an ependymoma had been partially removed from the right lateral ventricle. Left hemiparesis resulted from the tumor. One week before admission, the patient fell off her bed. Three days later she had nausea, epigastric discomfort, vomiting, nuchal rigidity and fever, with a temperature of 103 to 104 F.

Examination revealed that she was mentally cloudy and restless. The right big toe was swollen and red, with pus on the medial side of the nail. The Kernig sign was positive, and there was pain in the back of the neck on moving.

The fasting blood sugar was 180 mg. per 100 cc.; the white cell count was 13,350, with 79 per cent segmented granulocytes and the urine contained albumin and gave a 3 plus reaction for acetone. A lumbar puncture yielded cloudy cerebrospinal fluid with 640 segmented granulocytes. A direct smear of the cerebrospinal fluid showed gram-positive cocci. Culture of the cerebrospinal fluid failed to yield growth. However, from the blood culture a Staph. aureus was isolated twice. The organism was sensitive to bacitracin and resistant to penicillin, streptomycin, aureomycin and chloramphenicol.

Into the lumbar subarachnoid space, 10,000 units of bacitracin in 5 cc. of isotonic sodium chloride solution was immediately instilled. In addition to the intraspinal bacitracin therapy, the patient received intramuscular injections of procaine penicillin G, 600,000 units every 12 hours, and bacitracin, 10,000 units, and streptomycin, 0.5 Gm., every six hours. On the second day of treatment the cell count of the cerebrospinal fluid increased to 3,500 with 96 per cent segmented granulocytes. On the third day, 6,100 red blood cells appeared in the cerebrospinal fluid, in addition to 1,900 white blood cells. On the tenth day diabetic acidosis developed, and the patient went into coma as a result of inadequate insulin treatment. The dose of insulin was increased, and two days later she had insulin shock. Insulin therapy was readjusted, and on the next day she was alert. Her cerebrospinal fluid contained 1,370 white blood cells and 1,600 red blood cells. One day later the count dropped to 500 white cells. On the fifteenth day of treatment, the intraspinal injection of bacitracin was stopped. Three days later the cell count

2. Hoyne, A. L., and Brown, R. H.: Staphylococcic Meningitis: Its Rarity in the Newborn: Review of the Literature, Arch. Pediat. **65**:175-182, 1948.

of the cerebrospinal fluid was 180 per cubic millimeter. However, she still had a fluctuating low grade fever, although the blood culture had been repeatedly sterile and the infection of her toe had long been healed. On the twenty-fifth day, use of procaine penicillin G was changed to that of regular penicillin, 500,000 units every three hours for three days, and then back again. Streptomycin was discontinued on the twenty-sixth day. The intramuscular injections of bacitracin were continued until the thirty-eighth day, by which time the temperature was normal.

During the course of treatment with antibiotics by intramuscular injections, the cerebrospinal fluid continued an antibiotic level equivalent to 0.57 unit of penicillin. The urine gave a 1 or 2 plus reaction for albumin with a few white blood cells and occasional granular casts. Nevertheless, there was no change in the blood urea nitrogen. On December 16, the patient was transferred to Bellevue Hospital. Her cerebrospinal fluid still contained red blood cells, but it was clear.

This case illustrates the effectiveness of combined antibiotic therapy in meningitis with staphylococcic septicemia. Bacitracin was given by intraspinal injection for 15 days, without ill effect. The intraspinal therapy was supplemented with intramuscular injections of streptomycin, penicillin and bacitracin. The portal of entry of infection in this case was probably her infected right big toe. The organism entered the blood and involved the meninges, even though a positive culture of the cerebrospinal fluid was not obtained. Possibly the organism was anaerobic.

BACITRACIN

The active principle of bacitracin, described by Johnson, Anker and Meleney in 1945, is produced by the Tracy I strain of Bacillus subtilis.[3] It has a wide antibacterial spectrum, being effective against most strains of hemolytic and nonhemolytic streptococci, coagulase-positive staphylococci, pneumococci and anaerobic cocci in general, all of the gas gangrene group or organisms and the spirochetes of syphilis and mouth spirochetes, and among the protozoans, the Endamoeba histolytica.

In animals and in patients with normal meninges following the intramuscular injection of 10,000 units, small amounts of bacitracin may be found in the cerebrospinal fluid.[4] In the presence of meningitis in dogs and in patients a much higher concentration of bacitracin can be found in the cerebrospinal fluid after intramuscular injection.[4b]

Intracisternal injection of 10,000 units of bacitracin in 3 cc. of isotonic sodium chloride solution into dogs of 7 to 10 Kg. body weight produced

3. Johnson, B. A.; Anker, H., and Meleney, F. L.: A New Antibiotic Produced by a Member of the B. Subtilis Group, Science **102**:376-377, 1945.

4. (*a*) Scudi, J. V.; Coret, I. A., and Antopol, W.: Some Pharmacological Characteristics of Bacitracin: III. Chronic Toxicity Studies of Commercial Bacitracin in Dog and Monkey, Proc. Soc. Exper. Biol. & Med. **66**:558-561, 1947. (*b*) Teng, P., and Meleney, F. L.: Bacitracin Levels in the Cerebrospinal Fluid After Parenteral Injection: Bacitracin Therapy of Experimental Staphylococcic Meningitis in Dogs, Surgery **27**:403-413, 1950.

no ill effects except for transient rigidity of the neck, pleocytosis and an elevation of body temperature of 1 to 3 degrees (F.) All animals receiving injections survived, and none showed any abnormal neurological signs.[5]

The intraventricular or intracerebral injection of 5,000 units of bacitracin in 0.5 cc. of isotonic saline solution in cats of from 2.5 to 3.0 Kg. body weight is epileptogenic, but it does not kill the animals, and recovery is usually prompt and complete.[5] Five thousand units of bacitracin (50 units per milligram) in powder form when applied to the cerebral cortex produced convulsions in some of these animals, but they all survived.[6] A similar dose of penicillin when applied to or injected into the cortex experimentally regularly produced fatal status epilepticus in cats and monkeys. Five hundred units of penicillin in 0.05 cc. of isotonic sodium chloride solution by intracortical injection in monkeys has produced seizures.[7]

In the experiments with hemolytic Staph. aureus meningitis in dogs, the intracisternal injection of 5,000 to 10,000 units of bacitracin, one to 5½ hours after the inoculation of approximately 500,000,000 organisms by the same route, saved 75 per cent of the meningitic animals. All animals survived when treatment was started one to three hours after the bacterial inoculation. All control dogs died within 6½ hours after the intracisternal injection of bacteria. Another group of meningitic dogs was treated by intramuscular injections of bacitracin alone, and all animals invariably died about the same time as the controls.[4b] On the basis of these experiments, bacitracin was used in the treatment of human meningitis caused by the susceptible organisms, and promising results were obtained as outlined in the case histories above.

In the adult patient, 5,000 to 20,000 units of bacitracin in 3 to 5 cc. of isotonic sodium chloride solution can be safely injected intraspinally once or twice a day for two weeks with no untoward effects. Also, 3,000 to 10,000 units in 10 cc. of isotonic sodium chloride solution, injected into the lateral ventricle at 12 hour intervals, has been well tolerated. Furthermore, no ill effects were produced when 5,000 to 10,000 units in 10 cc. of isotonic sodium chloride solution was applied to a freshly cut cortical surface of the cerebral hemisphere in the prefrontal region as a postoperative prophylactic measure. A dose as large as 50,000 units in 5 cc. of isotonic sodium chloride has been given to a patient by intracerebral and intraventricular injection or applied to an ablated cortical

5. Teng, P.: Data to be published.

6. Cone, W.: Personal communication to the author.

7. Walker, A. E.; Johnson, H. C., and Kollros, J. J.: Penicillin Convulsions: The Convulsive Effects of Penicillin Applied to the Cerebral Cortex of Monkey and Man, Surg., Gynec. & Obst. **81**:692-701, 1945.

surface, and no bad effects have been noted.[5] A dose larger than this has not been used. Clinically, a dose larger than 10,000 units for local application to the central nervous system is not necessary.

On the basis of the past clinical experience in the treatment of infections of the central nervous system in 50 consecutive cases, the dosage for intraspinal, intraventricular, intracisternal and intracerebral injection of bacitracin in patients of different ages is summarized in (table 2).

Blood serum, pus or penicillinase produced by gram-negative microorganisms does not inhibit the action of bacitracin.[8] Nothing similar to penicillinase has yet been found which inactivates bacitracin, and hypersensitivity to this antibiotic is still unknown.[9] Furthermore, the penicillin-resistant strains of cocci are often found to be sensitive to bacitracin.

TABLE 2.—*Dose of Bacitracin for Local Application to the Central Nervous System*

	Route of Injection, Units (Bacitracin)			
Age, Yr.	Intraspinal	Intraventricular	Intracisternal	Intracerebral
Below 1	500-1,000	250-500	250-500	250-500
1 to 2	1,000	500	500	500
3 to 4	2,000	1,000	1,000	1,000
5 to 6	3,000	1,500	1,500	1,500
7 to 8	4,000	2,000	2,000	2,000
9 to 10	4,000	2,000	2,000	2,000
11 to 12	5,000	2,500	2,500	2,500
13 to 14	5,000	2,500	2,500	2,500
15 and over	10,000	10,000	10,000	10,000

However, it must be pointed out that some strains of staphylococci and streptococci are not susceptible to bacitracin. With some of these resistant strains a strong synergism of penicillin and bacitracin may sometimes be demonstrated.[10]

Certain of the earlier commercial preparations of bacitracin were found irritating to the kidneys after intramuscular injection, but this effect is much reduced with the present purified product, which may be safely given in doses of from 10,000 to 20,000 units every six to eight hours. Patients who have received only repeated intracranial or subarachnoid injections of bacitracin showed no urinary disturbance whatsoever.[5]

8. Meleney, F. L., and Johnson, B.: Bacitracin Therapy: The First 100 Cases of Surgical Infection Treated Locally with the Antibiotic, J. A. M. A. **133**: 675-680 (March 8) 1947.

9. Meleney, F. L.; Longacre, A. B.; Altemeier, W. A.; Reisner, E. H.; Pulaski, E. J., and Zintel, H. A.: The Efficacy and the Safety of the Intramuscular Administration of Bacitracin in Various Types of Surgical and Certain Medical Infections, Surg., Gynec. & Obst. **89**:657-683, 1949.

10. Johnson, B. A.: Personal communication to the author.

SUMMARY

During the past two years, 13 patients with purulent meningitis—staphylococcic, 6; streptococcic, 2; pneumococcic, 1; mixed infection, 2, and unidentified gram-positive cocci, 2—have been treated with bacitracin.

The causative organisms found to be resistant to penicillin and/or other antibiotics in 10 patients were so proved either by laboratory or by clinical observations.

Of eight patients who were treated with bacitracin after penicillin and/or other antibiotics and sulfonamides had failed, 6 survived and may be called salvaged. Five patients were treated primarily with bacitracin by intracranial and subarachnoid therapy, supplemented with systemic use of penicillin and bacitracin and 3 recovered. Thus, in a small series of 13 patients with purulent meningitis treated by this combined antibiotic therapy, 9 recovered, a survival rate of approximately 70 per cent. Of the surviving patients, the youngest was 6 weeks and the oldest 76 years of age.

Of the 4 deaths, one was from an irremovable tumor in the pineal region, which caused complete block of the ventricular system and meningitis; one from thrombosis of the middle cerebral artery with extensive cerebral infarction and infection of the brain tissues; one from multiple brain abscesses and a long-standing, extensive purulent encephalitis, and one from an undisclosed brain abscess, diffuse encephalitis, extensive bronchopneumonia and cardiac failure.

1 East One-Hundredth Street.

News and Comment

AMERICAN ACADEMY OF NEUROLOGY

The meeting of the American Academy of Neurology is scheduled for April 11 to 13, 1951, at the Cavalier Hotel, Virginia Beach, Va. It will be preceded by a two day course in neuropathology and will be followed by the 1951 meeting of the American Chapter of the International League Against Epilepsy.

CONTINUATION COURSE IN CLINICAL NEUROLOGY

Distinguished physicians who will participate as faculty members in a continuation course in clinical neurology to be presented by the University of Minnesota at the Center for Continuation Study from Jan. 29 to Feb. 10, 1951, are as follows: Dr. Pearce Bailey, Georgetown University School of Medicine, Washington, D. C.; Dr. H. W. Magoun, University of California Medical School; Dr. Henry Schwartz, Washington University School of Medicine, St. Louis, and Dr. S. Bernard Wortis, New York University Medical Center. Dr. Magoun will also deliver the annual J. B. Johnston Lecture; his subject will be "Wakefulness and Sleep."

SPECIAL NOTICE

For the general information of indexers, catalogers and library personnel with reference to the listing of the new title of this journal, we advise that the *Quarterly Cumulative Index Medicus* policy be followed. The *Quarterly Cumulative Index Medicus* with its volume 49 (January-June 1951) will list this journal under the new title, so that the letters A. M. A. will be included as an integral part of the title. For the completion of volume 48 (July-December 1950) the *Quarterly Cumulative Index Medicus* will continue to use the old title, without adding the designation A. M. A.

CORRECTION

The work of Lowenstein and Loewenfeld on "Role of Sympathetic and Parasympathetic Systems in Reflex Dilatation of the Pupil" and "Mutual Role of Sympathetic and Parasympathetic in Shaping of the Pupillary Reflex to Light," published in the September 1950 issue of the ARCHIVES, pages 313 and 341, respectively, was aided by grants from the Harriman Fund and the Milbank Memorial Fund. In these publications, the second organization was incorrectly called the Duntery Milbank Foundation on page 313, and the Milbank Foundation on page 341.

In the article by Dr. Hubert Csermely entitled "Demyelinating Encephalomyelitis Following Use of Antitetanus Serum," published in the November issue of the ARCHIVES, lines 10 and 11, page 676, should read ". . . a neurotropic virus from the blood in one case of encephalomyelitis and from the brain tissue in another." In line 2 of the "Summary," page 684, "1,500" should be "2,500."

The publisher of Gagel's "Einführung in die Neurologie: Bau und Leistung des Nervensystems unter normalen und pathologischen Bedingungen" and of Ostertag's "Die Sektion des Gehirns und Rückenmarks und ihre Hüllen" is Springer-Verlag, Berlin-Göttingen-Heidelberg, not Springer-Verlag, Vienna, as was stated in the August issue, page 311, and the September issue, page 488, respectively.

Obituaries

ADOLF MEYER, M.D.

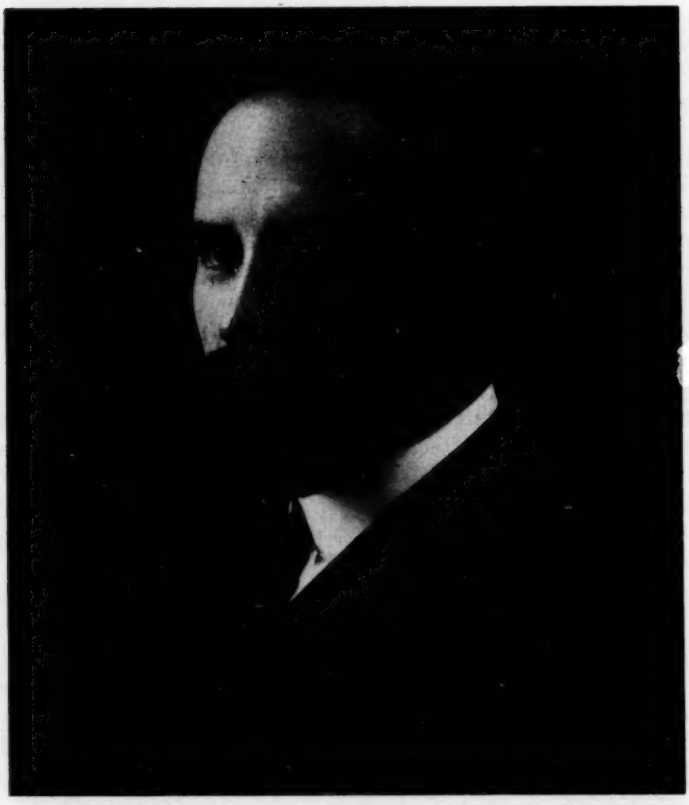
1866-1950

Adolf Meyer was an editor of the ARCHIVES from 1929 until his death, in March 1950. This was only one facet of a life filled to overflowing with activities related to psychiatry: therapy, research, teaching and public service. There is no need to give a detailed account of his professional life. This has been well done by Alfred Lief in his book, "The Commonsense Psychiatry of Adolf Meyer" (New York, McGraw-Hill Book Co., Inc., 1948), which was compiled during Dr. Meyer's later years and reprints most of his more important papers. His complete works are to be published shortly by the Johns Hopkins Press. This will be a four volume record of the writings of a man whose mind was continuously working smoothly on important problems and whose published works prove his great productiveness. He was a perfectionist in the sense that he wanted his ideas exactly expressed, and, being a versatile scholar and philosopher of great wisdom, this exact exposition was often complex. It was this desire for fairness and honesty to all sides of a question that made some of his lectures and writings difficult to grasp. But he knew the subject was complex and difficult and had little use for the popular simplifications that did not hew to the line of truth.

Few people know what a fine psychotherapist Dr. Meyer was. But those who were fortunate to be his patients and house staff knew it well. To make a ward visit with him and treat patients under his guidance was a great privilege that made a young man develop the best in himself. Ward visits were also fun, because the Professor had a gay quality and warm sense of humor that lightened the day's work and saved his pupils from being depressed by the tragedy that often surrounded them. To see him interview a new patient and, with few words, but manifest, quiet sympathy, reach the heart of a problem was a lesson never forgotten.

Great as was Meyer's contribution by teaching individual assistants, even greater was his influence as lecturer and writer. As early as 1897 his dynamic psychiatry was persuading psychiatrists to advance from the classic kraepelinian point of view and look on a mental disease as a disorder of the person. To Meyer all life was reaction; the person was to be studied with the methods of anatomy, physiology and psychology. One "cannot afford to disregard any side of the biological unit in the patient." Thus, before 1900 the basis for psychosomatic medicine was

propounded, and the dynamic psychology of Meyer prepared America to understand Freud. Fifty years later Meyer was still insisting that psychiatrists take, as their object of study, the "he" and the "she," the person as a whole, without undue emphasis on any part, such as the "ego" or the "unconscious." He appreciated Freud's great contribution, pointing out that it was as important to psychopathology as dietetics was



ADOLF MEYER, M.D.
1866-1950

to medicine. But he considered psychoanalysis a partial and esoteric system, which engendered a spirit of denominationalism and bred controversy.

He did not believe in polemics, but he held steadfastly to his principles. Long after he and Freud had won the battle for psychogenesis

against Kraepelin he kept on teaching the necessity for his holistic approach to psychiatry, for he knew how comfortable it is for the physician to fall back on "degeneracy" and "disease" as responsible for abnormal behavior, instead of "accepting these conceptions which make the physician partly responsible for the plain and manageable facts." This phrase comes from his remarkable paper, "The Dynamic Interpretation of Dementia Praecox," delivered at Worcester in 1909, when he and Freud met at that extraordinary assembly at Clark University and both received degrees.

In 1944 he urged "a frank pluralism and empirical objectivity with an honest respect for the real *person* and *group* as *units*. As individual and group psychiatry has taught us, this requires the principle of dealing with individual wholes and group wholes including also subunits and their parts, in harmony with good sense, science, philosophy and religion: *first* and above all things, *good sense,* with its *vigor* of hygiene and meliorism and essential respect for relations; then *second, science* as intension and extension, with the smallest number of assumptions for search and research and reference to specific systems; *third, philosophy,* as concern for perspective, and recognition of a world of synonyms and antonyms, but operational principles of interrelations; and *fourth, religion* as a way of trust and reciprocal *obligations* as well as *dependabilities* in life." This quotation is an example of Meyer's writing—difficult on the first reading but richly rewarding to one who will read again and cogitate.

In the early years there was research of problems on anatomy of the brain, aphasia and sensory deficit. The experiments performed by nature through trauma and disease were ever exciting to Meyer. In fact, research to him was not something set off from practice and honored with a capital R. All patients brought facts to him; guiding a clinic and treating patients were as important for research as for therapy and education. He was indeed an integrated man, a harmonious person. His place in the history of medicine and psychiatry is assured. The memory of his sincerity, warmth and understanding will live in the hearts of his pupils as long as that fortunate generation survives.

STANLEY COBB, M.D.

Boston

C. CHARLES BURLINGAME, M.D.

1885-1950

Last July C. C. Burlingame went to England, where he was to receive honorary membership in the Royal Medico-Psychological Association. On July 22, as the result of two coronary occlusions, he died in a private hospital in Leicester. Two months before, he had been made president-elect of the Connecticut State Medical Society.

Dr. Burlingame was born in Rockford, Ill., on Oct. 27, 1885. He received his early education in the public schools in Rockford and in 1908 gained the degree of Doctor of Medicine from the Hahnemann Medical College and Hospital in Chicago. From 1908 to 1912 he served as assistant physician in the Westboro (Mass.) State Hospital and then moved to the Fergus Falls (Minn.) State Hospital, where he stayed until 1915, first as assistant superintendent and later as acting superintendent.

In 1915 he started his career in industrial medicine as psychiatrist in a silk mill in Manchester, Conn. Here the work was much to his liking, as he had a real flair for organization and administration, which were to be his main contribution to medicine and psychiatry.

In 1917, when this country entered World War I, the American Red Cross was hard put to it to find someone to run its office in Paris and administer its far-flung interests. In Burlingame it found just the man it wanted. Very soon he had that service running smoothly, and for the excellent work he did there the French government awarded him the Legion of Honor and the United States Army cited him for "conspicuous and meritorious service." He likewise received medals from Poland and Czechoslovakia.

The war over, Burlingame returned to New York, expecting again to take up his work in industrial psychiatry, but found instead another administrative job awaiting him. The Columbia-Presbyterian Hospital Medical Center was then in the making, and a man was needed to organize that work and get it running smoothly. Again, Burlingame was the man for the job, and he fitted in well to one of the most difficult positions a medical administrator ever held. The work was done with Burlingame's usual efficiency; the Medical Center was built and running well, and Burlingame was looking for a new job.

He did not have long to wait. The directors of the Hartford Retreat needed someone to modernize that century-old mental institution. It could hardly have been called a hospital then. Burlingame transformed

it into one of the foremost psychiatric hospitals in the country. Adding the name "Institute of Living" to the old one, he started in a monumental chore of modernization. He enlarged the staff with a lavish hand, built many new buildings and brought to the old institution the recognition it deserved. The hospital was his hospital. Not only was he medical director and psychiatrist in chief, but he was also president of the institution and chairman of its board of directors. The Burlingame spirit permeated the whole institution and made it what it is today.

It would be tiresome to repeat here the names of all the medical and other societies to which Dr. Burlingame belonged. They include many of the psychiatric and other medical societies in this country. He was associate in psychiatry in Columbia University College of Physicians and Surgeons and for a while held the position of clinical professor of psychiatry at Yale University. From its start he headed the Salmon Memorial Committee of the New York Academy of Medicine. Many hospitals of all sorts appointed him consulting psychiatrist. He was a member of a dozen or more clubs of various kinds.

C. C. Burlingame will be remembered in American medicine as an able and accomplished administrator who could be relied on to make a success of any medical administrative job he attempted. His friends will remember him as a genial, kindly fellow, with a wealth of good nature, a ready bubbling laugh and an inexhaustible store of enthusiasm for any job he was asked to tackle.

LOUIS CASAMAJOR, M.D.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Physiology and Biochemistry

ELECTROCORTICOGRAPHY. C. MARSHALL and A. E. WALKER, Bull. Johns Hopkins Hosp. **85**:344 (Nov.) 1949.

The recording of the electrical changes in the brain by electrodes placed directly on the cerebral cortex has been termed electrocorticography. The authors describe the model of the electrode holder and the technic of investigation used in the present study.

The tracings obtained from the exposed cerebral cortex differ from those obtained from the scalp in two main characteristics: 1. The amplitude of the cortical activity is three to four times as great as that of activity sampled through the calvarium and scalp. 2. Rapid oscillations in electrical activity are not distorted in the electrocorticogram and hence appear as spikes.

It has been said that the electrocorticogram is dependent on the cytoarchitectural structure of the cortex and that different areas have typical frequencies and patterns. Marshall and Walker state that, although at times it may be possible to recognize an area by its rhythm, as a rule, under controlled conditions, such prediction is no better than chance.

Anesthesia plays a great role in the characteristics of the electrical activity. In the authors' experience, ether anesthesia causes a pronounced slowing of the cortical frequencies with some increase in amplitude. This effect is present in all regions of the brain. Such slow activity obscures all normal alpha rhythm and seems to depress the general excitability of the cerebral cortex, so that epileptic discharges are suppressed and rarely seen. Thiopental anesthesia, at least in the surgical planes, augments the frequency and amplitude from all cortical regions. It does not seem to depress the cortical activity unduly, for epileptic discharges may still be seen. In general, the most accurate results can be obtained from electrocorticography when the craniotomy is done with the use of local anesthesia, but at times satisfactory results may be obtained with general anesthesia. Morphine, in the doses usually employed to allay anxiety, does not seem to depress cortical activity.

The authors state that electrocorticographic studies may be carried out in the ordinary operating room if certain precautions are taken. Many characteristics of cortical physiology in man, especially those associated with convulsions, may be explored by electrocorticographic recording. Subcortical tumors of the brain may be localized by the presence of slow wave activity over the tumor.

Electrocorticography is particularly valuable in the localization of epileptic foci. Cortical exploration should be carried out with the use of local anesthesia. The epileptogenic focus may be determined by (1) focal spontaneous spiking, (2) induction of a convulsive aura by the electrical stimulation of the cortex, (3) production of a long-lasting after-discharge and (4) initiation of spiking by local or systemic administration of metrazol.®

ALPERS, Philadelphia.

THE FATE OF AN INTRANEURAL INJECTION AS DEMONSTRATED BY THE USE OF RADIO-ACTIVE PHOSPHORUS. J. B. BRIERLEY and E. J. FIELD, J. Neurol., Neurosurg. & Psychiat. **12**:86 (May) 1949.

Brierley and Field injected 0.05 ml. of radioactive phosphorus into the sciatic nerve of the rabbit to determine the distribution of this substance in the blood.

cerebrospinal fluid and nervous system. The results were compared with those in control animals in which the substance was injected intravenously. It was found that the type of injection determined whether there was a high count in the cerebrospinal fluid and central nervous system or a high concentration in the blood. The injections fell into two types: (1) a "cord–cerebrospinal fluid" type, characterized by minimal resistance to injection, absence of dilatation of the nerve, spread of the indicator centrally through the nerve and spinal cord, entry of the indicator into the cerebrospinal fluid and relatively little absorption into the blood stream, and (2) a "blood" type, in which there was considerable resistance to injection, variable dilatation of the nerve, limited spread of the indicator within the nerve and none into the cord, no entry into the cerebrospinal fluid but considerable absorption into the blood stream. The authors concluded that the "cord–cerebrospinal fluid" type of injection can be attributed to the penetration of the fasciculus by the needle point, whence spread took place along the interfiber spaces. On the other hand, in the "blood" type of injection, the needle point lay within the perineurium, with only slight penetration into the fasciculus. When applied to disease-producing experiments, such as with the virus of poliomyelitis or tetanus toxin, the end result depends on which type of intraneural injection occurred. The authors also emphasize the importance of the perineural space and lymphatics as methods of spread along the nerve bundles rather than through the periaxonal pathway, neurilemma or myelin sheath.

N. MALAMUD, San Francisco.

ELECTRICAL ACTIVITY OF THE NEOSTRIATUM, PALEOSTRIATUM, AND NEIGHBOURING STRUCTURES IN PARKINSONISM AND HEMIBALLISMUS. RUSSELL MEYERS, ROBERT HAYNE and JOHN KNOTT, J. Neurol., Neurosurg. & Psychiat. **12**:111 (May) 1949.

Meyers and his associates recorded electrograms from the striatum and neighboring structures in 10 cases of parkinsonism and in 1 case of hemiballismus. They compared their findings with the electrograms of 11 control subjects. Their recordings consisted of monopolar and bipolar readings. The results indicated that there is no characteristic dysrhythmia or change in frequency or wave amplitude associated with these diseases. This observation was contrary to a previous report based on 1 case, in which a characteristic slow wave and low amplitude record was obtained. The authors also found no apparent relation between the electrical activity of the corpus striatum or neighboring structures and the presence or absence of electromyographic activity associated with tremors.

N. MALAMUD, San Francisco.

RESPIRATION AND GLYCOLYSIS OF FOCAL EPILEPTOGENIC HUMAN BRAIN TISSUE. K. A. C. ELLIOTT and W. PENFIELD, J. Neurophysiol. **11**:485, 1948.

Elliott and Penfield studied the average rate of oxygen uptake of samples of human cerebral cortex. The cortex was epileptogenic and had been resected to relieve the patients of seizures. They concluded that the average rate of oxygen uptake was not significantly different from that of normal human cortex. The relative rates of oxygen uptake, carbon dioxide evolution and aerobic and anaerobic glycolysis were not significantly different in focal epileptogenic tissue than in normal brain tissue.

FORSTER, Philadelphia.

RETICULO-SPINAL INFLUENCES ON STRETCH REFLEXES. J. M. SPRAGUE, L. H. SCHREINER, D. B. LINDSLEY and H. W. MAGOUN, J. Neurophysiol. **11**:501, 1948.

The authors studied the electromyograms of decerebrated cats before, during and after electrical stimulation of nuclei of the brain stem. The decerebrate state consists in an exaggeration of stretch reflexes in the antigravity muscles. Electrical stimulation of the reticular substance of the brain stem resulted in the exertion of strong facilitatory and suppressor influences on the stretch reflexes. The influences are generalized and are exerted on both flexor and extensor mechanisms. Vestibular influences are ipsilateral and facilitatory and are evoked by low frequencies of stimulation. Cerebellar influences are suppressor and evoked by high frequency of stimulation.

FORSTER, Philadelphia.

THE CONVULSIVE EFFECTS OF STREPTOMYCIN TOPICALLY APPLIED TO THE CEREBRAL CORTEX. HENRY M. SUCKLE, ROLAND R. LIEBENOW and O. SIDNEY ORTH, J. Neurosurg. **4**:370 (July) 1947.

Suckle, Liebenow and Orth investigated the convulsant effect of streptomycin applied directly to the cerebral cortex of experimental animals. They found that (1) streptomycin exerts a local effect on the cerebral cortex, causing convulsive action; (2) the immature cortex is more likely to show a convulsive reaction to the irritating streptomycin; (3) the convulsive reaction is proportional to the antibiotic potency of the drug; (4) the intrathecal injection of streptomycin should be limited to 50,000 units (50 mg.) per injection, diluted in 10 to 20 cc. of isotonic sodium chloride solution.

TOZER, Philadelphia.

THE NERVOUS PATHWAY OF THE PSYCHO-GALVANIC REFLEX. KENNETH W. GOADBY and HECTOR K. GOADBY, J. Physiol. **109**:177, 1949.

The psychogalvanic reflex is described as consisting of changes in electrical potential of the skin (the potential response) and changes in electrical resistance of the body (the resistance response), associated with psychic or emotional stimuli. Simultaneous records of the potential and the resistance response of the pschogalvanic (psychomotor) reflex were made on human subjects. Such records made on 7 patients before and after operation showed that sympathectomy abolished both the responses in the limb operated on. Complete exsanguination of the limb abolished the resistance response while leaving the potential response intact. In a case of complete transection of the spinal cord at the eighth thoracic level, the responses in all four limbs were normal.

The afferent and efferent pathways of the psychogalvanic (psychomotor) reflex are discussed, with a review of the literature. It is postulated that the basis of the resistance response is a change in the vascular bed and that the basis of the potential response is actively at the sympathetic nerve endings.

THOMAS, Philadelphia.

EFFECT OF PRESSURE ON NERVE CONDUCTION AND NERVE-FIBRE SIZE. G. CAUSEY and E. PALMER, J. Physiol. **109**:220, 1949.

Local application of pressure, by means of mercury, to a nerve caused failure of the nerve to conduct an impulse to the muscle when the stimulus was applied above the site of pressure. All pressures above 150 mm. of mercury produced block. The average time required to obliterate the muscle response was twenty minutes. Recovery of conduction took place within five to sixty-five seconds after the

release of pressure and the admission of air. Nerve fiber size and nerve bundle size were diminished at the site of pressure, and there was recovery of nerve fiber size and nerve bundle size ten minutes after the release of pressure. Application of pressure by air had not produced failure in conduction of an impulse in fifty-two minutes. The circulation of the blood was stopped by ligature of the aorta and pulmonary artery at the base of the heart. After this was done, it was still possible to block conduction along the nerve by localized pressure, and to obtain recovery on the release of pressure, before the final death of the preparation. It is concluded that in acute experiments the failure of the nerve to conduct an impulse after local pressure is caused by local anoxia.

THOMAS, Philadelphia.

INTRATHECAL ADMINISTRATION OF CARBON DIOXIDE AND ITS EFFECT ON CEREBRAL CIRCULATION. DIEGO BRAGE, Prensa méd. argent. **33**:1838 (Sept. 6) 1946.

Carbon dioxide in the spinal fluid is well tolerated, even in large doses. In concentrations of less than 5 per cent, it has a beneficial effect on the circulation of the nervous system by causing vasodilatation of cerebral blood vessels. No complications were observed in numerous instances after the administration of carbon dioxide intrathecally. Without giving any actual data (presented in other publications), Brage reports notable improvement in patients with cerebral anoxia. The reaction to carbon dioxide is enhanced by the administration of oxygen at the same time. Carbon dioxide apparently acts directly on the blood vessels, as well as on the vasomotor centers in the medulla.

SAVITSKY, New York.

Neuropathology

DIFFUSE SCLEROSIS OF A DEGENERATIVE TYPE. R. DUBOIS and R.-A. LEY, Acta neurol. et psychiat. Belg. **49**:13 (Jan.) 1949.

Dubois and Ley report the case of a boy aged 4 years with a chronic progressive paralyzing disturbance characterized by generalized hypertonicity, spastic paralysis of all four extremities, strabismus, facial paresis, incontinence and intention tremor, but with preserved hearing. Pathologic studies showed diffuse demyelination, which was most intense in the motor and parietal regions but was present also throughout the centrum ovale, the temporal lobes, the corpus callosum and the internal capsule. Within the spinal cord the most pronounced degeneration was in the crossed pyramidal tracts. Because of the destructive characteristics without evidence of repair, the authors speak of this condition as a degenerative type of diffuse sclerosis.

DEJONG, Ann Arbor, Mich.

ANATOMIC AND CLINICAL STUDY OF POSTVACCINAL ENCEPHALITIS. M. GRAFFAR, R.-A. LEY and F. LHERMITTE, Acta neurol. et pyschiat. Belg. **49**:25 (Jan.) 1949.

Twelve days after his first vaccination, a boy aged 9 years had onset of headache and fever. The respiration became rapid and feeble, the pulse irregular and the extremities flaccid, and loss of consciousness developed. The patient died three days later. The spinal fluid contained 50 cells per cubic millimeter, of which 55 per cent were lymphocytes, 5 per cent monocytes and 40 per cent segmented granulocytes.

Pathologic studies showed extensive involvement of the white matter of the hemispheres with perivascular infiltration, glial proliferation and perivascular demyelination. The cerebral cortex presented many areas of perivascular infil-

tration. The thalamus showed secondary degeneration. The basal ganglia and subthalamic nucleus exhibited pronounced vascularity. There were moderate alterations in the cerebellum and pons and no changes in the medulla. The inflammatory reaction seemed to be the major pathologic change, and the demyelination was secondary to this.

DeJong, Ann Arbor, Mich.

Histopathologic Study of a Cystic Papilloma of the Choroid Plexus of the Third Ventricle. M.-A. Gerebtzoff and E. Nizet, Acta neurol. et psychiat. Belg. **49**:453 (July) 1949.

Gerebtzoff and Nizet describe a cystic papilloma of the choroid plexus of the third ventricle in a man aged 49. The principal symptoms were those of hypothalamic involvement, namely, somnolence and intracranial hypertension. Careful histologic studies are necessary to differentiate a tumor of this type from other papillary or cystic tumors in the region of the third ventricle, notably the papillary ependymoma.

DeJong, Ann Arbor, Mich.

Diseases of the Brain

Epilepsy in Twins: An Analysis of Five Twin Pairs, with Electroencephalographic Studies. S. C. Little and N. K. Weaver, Am. J. Dis. Child. **79**:223 (Feb.) 1950.

Studies of twin pairs are of great importance in evaluating the influence of "heredity" and "environment" in the production of convulsive disorders. This report is a detailed analysis of the data on five twin pairs.

In the dizygotic pairs inheritance was dissimilar. Of the pair with a family history of epilepsy, both members had seizures and cerebral dysrhythmia, but of different types. Of the pair without a family history of epilepsy, only one had cerebral dysrhythmia and seizures, the type of dysrhythmia suggesting that the disorder might be "symptomatic."

In the three monozygotic pairs inheritance was identical. Only one member of each pair had seizures. In pair 1 there was no family history of seizures and the influence of heredity was negligible, as the seizures of the affected twin appeared to be the result of acquired cerebral disease. In pairs 2 and 3 there was a family history of epilepsy, and the electroencephalograms of the members of each pair were similar. It is pointed out that the convulsive disorder in the affected members of pairs 2 and 3 was relatively mild, and this may account for lack of clinical seizures in the co-twins in each case.

The results of the analysis of this small series confirm the previously expressed opinion that epilepsy and cerebral dysrhythmia may be either inherited or acquired. An inherited predisposition to epilepsy, as manifested by cerebral dysrhythmia, is not necessarily synonymous with clinical seizures. The usefulness of electroencephalographic studies in determining the presence or absence of hereditary factors in the causation of epilepsy is confirmed by this study.

Alpers, Philadelphia.

Intracranial Venous Thrombosis in the Puerperium, H. H. Hyland, J. A. M. A. **142**: 707 (March 11) 1950.

Hyland reports 2 cases of intracranial thrombosis occurring in the puerperium, In both, symptoms appeared within two weeks after normal delivery. The early signs include headache and focal or generalized convulsions, followed by monoplegia

or hemiplegia with or without aphasia, and occasionally by bilateral involvement of the limbs. Papilledema may be present, and amaurosis has been described. The occurrence of papilledema depends on whether there is severe obstruction of the superior sagittal sinus, in which event there will also be a decided elevation in the pressure of the cerebrospinal fluid. In neither of the cases reported was papilledema observed. In case 1 there was pronounced elevation of the cerebrospinal fluid pressure on the patient's admission to the hospital, but evidently the capacity of the superior sagittal sinus to absorb cerebrospinal fluid became rapidly reestablished, because the occlusion was mainly in its lower portion. The cerebrospinal fluid frequently shows no abnormality, but occasionally in the presence of extensive venous thrombosis small quantities of blood may be found and the total protein may be slightly elevated.

Both patients recovered from the cerebral symptoms, but one died subsequently of a pulmonary embolus. Attention is drawn to the remarkable degree of clinical recovery from the cerebral lesion which occurred in the presence of extensive thrombosis of the cerebral veins, with consequent residual cortical damage found at autopsy. The other patient had remained symptom free when last contacted, one and one-half years after the illness.

ALPERS, Philadelphia.

VISUAL SCOTOMATA WITH INTRACRANIAL LESIONS AFFECTING THE OPTIC NERVE. ALAN J. MOONEY and ADAMS A. MCCONNELL, J. Neurol., Neurosurg. & Psychiat. **12**:205 (Aug.) 1949.

Mooney and McConnell review the literature on the production of central visual scotomas by space-occupying intracranial lesions and report 7 cases. The current theories of the causation of central scotomas involve either the concept of direct pressure on the optic nerve and tract or that of interference with their blood supply. In the opinion of the authors, any pressure sufficient to involve the nerve fibers would necessarily disturb their blood supply and vice versa. It is generally assumed that a lesion compressing the optic nerve close to the optic foramen is particularly liable to be associated with central scotoma. This defect is considered due to obstruction of the ophthalmic artery, resulting in impairment of the papillomacular bundle, which has a relatively poor blood supply. However, such hypersensitivity of the bundle fails to explain the occurrence of either peripheral or central defects under similar conditions. On the hypothesis of vascular obstruction, the presence or absence of central scotomas depends on whether or not a particular vessel or group of vessels is involved. Obstruction of such vessels has not been demonstrated at operation or by angiography. The appearance at operation suggests that the obvious pressure on the nerve is related to the scotomatous defect, but it would seem that the problem is of a more complex nature.

N. MALAMUD, San Francisco.

LEPTOTHRIX AS A CAUSE OF BRAIN ABSCESS: REPORT OF TWO CASES. E. L. DOERMANN and T. C. ERICKSON, J. Neuropath. & Exper. Neurol. **8**:436 (Oct.) 1949.

Doermann and Erickson report 2 cases of cerebral abscess due to Leptothrix. A review of the literature has disclosed no reference to similar cases in man, although abscesses of the brain have been produced experimentally by this organism.

The first patient had a very large abscess of the left frontal lobe from which a pure culture of Leptothrix was grown. The evidence indicated a hematogenous origin rather than direct spread of infection from the paranasal sinuses or the middle ear. Adequate surgical drainage of the abscess was obtained and

maintained and was no doubt the most important factor in recovery. Sulfathiazole was used both locally and parenterally.

The second patient died, and a pure culture of Leptothrix was obtained from a cerebellar abscess. The unfavorable outcome was due to failure to maintain proper surgical drainage and to the occurrence of a secondary infection and pleural empyema. In these circumstances, penicillin, sulfathiazole and sulfadiazine were of no demonstrable value. The origin of the abscess in this patient might from its location be assumed to have been by direct spread from the middle ear or the mastoid. In view of a vague history of "lung congestion," it was also suspected that the cerebellar abscess was metastatic from a primary Leptothrix infection in the chest. Bacteriologic studies of the pleural fluid, however, failed to substantiate this point. The authors conclude that the route of infection was most likely hematogenous in this case also.

ALPERS, Philadelphia.

NEUROLOGIC LESIONS IN THE NEWBORN: I. PRELIMINARY STUDY. II. ROLE OF PROLONGED LABOR, ASPHYXIA AND DELAYED RESPIRATION. H. M. KEITH and M. A. NORVAL, Proc. Staff Meet. Mayo Clinic **25**:11 (Jan. 4) 1950.

In the first article, Keith and Norval report on a survey of 4,464 infants, 57 of whom (1.3 per cent) had primary neurologic lesions in the neonatal period. Seven infants were stillborn, of whom 5 were premature and anencephalic. Twenty-eight others of the 57 died before the age of 9 months. Six of those who died in the first week had a demonstrable intracranial hemorrhage, but all had been born without undue difficulty during labor. Twelve more infants died during the first week. Six of the 12 had gross neurologic abnormalities, such as anencephaly and hydrocephalus. Four were premature; 1 had erythroblastosis, and 1 died of "cerebral anoxia." Ten other babies lived for periods varying from eighteen days to eight months. Nine of the 10 infants had gross abnormalities, and 1 had a subdural hematoma. Of the 22 babies alive after 8 months of age, 2 were microcephalic, 6 had mongolism, 5 had gross neurologic abnormalities, 1 had multiple abnormalities and convulsions, 2 could not be traced and the remaining 6 are normal children, at ages varying from 1½ to 4½ years.

The authors conclude from their findings that difficulties during delivery had comparatively little to do with persistent neurologic abnormalities in the infants who survived.

In the second article, from the authors' series of 216 infants born after prolonged labor, it appears to be true that the difficulty of the labor increases the risk of cerebral injury and death. However, if one compares the infants who had "prolonged" deliveries with those who had "normal" deliveries, one finds little or no difference in the subsequent development of the infants who survived.

One hundred and eleven babies experienced asphyxia or delayed respiration or both. Anoxia caused by delay in the onset of respiration did not have a serious prognosis in those infants who survived the neonatal period. Even a delay of eleven to fifteen minutes, while fatal in 2 instances, did not appear to cause any abnormality, at least during the first four years of life, in the infants who survived.

ALPERS, Philadelphia.

CHROMOPHOBE ADENOMA IN A MALE AGED 15½ YEARS. S. LEONARD SIMPSON and WRIGHT A. DICKSON, Proc. Roy. Soc. Med. **40**:151 (Feb.) 1947.

A chromophobic adenoma with symptoms dating back two years was found at operation to extend downward into the sphenoidal fissure and raise the optic chiasm posteriorly. Roentgen therapy followed operation, and improvement in

ophthalmoplegia occurred; but the patient remained weak, apathetic and bedridden. Testosterone was given in injections of 25 mg. daily, with dramatic effect on appetite, sense of well-being, nitrogen retention and muscular strength.

BERRY, Philadelphia.

CHROMOPHOBE ADENOMA IN MALE AGED 67 YEARS. S. LEONARD SIMPSON and JULIAN TAYLOR, Proc. Roy. Soc. Med. **40**:151 (Feb.) 1947.

A chromophobic adenoma with symptoms dating back six years was removed at operation in a man aged 67. After operation, the patient complained of weakness, sensitivity to cold and lack of libido, with some loss of secondary sexual characteristics. Methyl testosterone, 10 mg. given sublingually three times a day, resulted in improvement, and after six weeks the patient was maintained on 5 mg. three times a day. Six years after operation, libido, potentia and secondary sexual characteristics had returned.

BERRY, Philadelphia.

CLINICAL STUDY OF MYOCLONIC EPILEPSY. J. CORDIER, A. DEWULF, D. LOUIS-BAR, J. RADERMECKER and G. SEGERS, Acta neurol. et psychiat. Belg. **49**:233 (April) 1949.

Myoclonic epilepsy may be divided into (1) classic epilepsy, in which the aura of the attack or the equivalents are represented by myoclonic movements, which may persist during the attack, and (2) juvenile encephalopathies, which have as their sequelae both convulsive manifestations and myoclonus. In either group the condition may be progressive, with final intellectual deterioration. The hyperkinetic phenomena may be either a sequel or a complication of either variety.

DEJONG, Ann Arbor, Mich.

HEREDITARY SPASTIC PARALYSIS ASSOCIATED WITH OLIGOPHRENIA AND CATARACT FORMATION. J. CORDIER and A. DELAEY, Acta neurol. et psychiat. Belg. **49**:621 (Sept.) 1949.

Cordier and DeLaey describe a patient aged 28 with spastic paralysis, defective cranial development, mental deficiency and centrally placed opacities of the crystalline lens. They express the opinion that the cataract formation is probably on the basis of endocrine change secondary to the encephalopathy.

DEJONG, Ann Arbor, Mich.

HEREDITARY SPINOPONTOCEREBELLAR DEGENERATION WITH RETINAL AND COCHLEOVESTIBULAR MANIFESTATIONS. J. FRANCOIS and L. DESCAMPS, Acta neurol. et psychiat. Belg. **49**:631 (Sept.) 1949.

Francois and Descamps describe a case of hereditary spinopontocerebellar degeneration accompanied with pigmentary degeneration of the retina, in which there was optic nerve atrophy, as well as deafness and vestibular disturbances.

DEJONG, Ann Arbor, Mich.

Treatment, Neurosurgery

PROLONGED SURVIVAL FOLLOWING STREPTOMYCIN THERAPY OF TUBERCULOUS MENINGITIS. H. S. TACKET and G. S. LOVEJOY, J. A. M. A. **142**: 648 (March 4) 1950.

It is known that streptomycin frequently prolongs the life of patients with tuberculous meningitis. Tacket and Lovejoy emphasize again, however, that

streptomycin therapy for tuberculous meningitis is far from satisfactory, since, even though the immediate results are promising, patients may succumb later to complications of the original infection.

The authors report a case of tuberculous meningitis in a boy aged 13, treated with streptomycin, in which there was restoration of ability for normal activity. He was readmitted eight months after the original illness, and complicating adhesive arachnoiditis was relieved by surgical intervention, with good results. Streptomycin was again administered, over a period of about four months.

For about fifteen months the patient was apparently well and attended school, where he made superior grades. However, he died twenty-seven months after the original attack of meningitis from reformation of arachnoidal adhesions, internal hydrocephalus and reactivation of meningeal tuberculosis.

ALPERS, Philadelphia.

REACTIONS FOLLOWING INTRACISTERNAL USE OF STREPTOMYCIN. F. E. VALERGAKIS, D. S. HAYS and A. M. SUTHERLAND, J. A. M. A. **142:** 720 (March 11) 1950.

The authors report the neurologic complications resulting from instillation of streptomycin after intracisternal injection in 2 cases. The patients were both adults, one with a condition diagnosed as tuberculoma, the other with tuberculous meningitis. In 1 case there was respiratory failure and death, and in the other coma was followed by a pronounced change in mental status for several days. These reactions are believed to have been due to a direct neurotoxic action of streptomycin on the medullary centers and the cerebral cortex, rather than to trauma or disease.

Valergakis and his co-workers believe that the intracisternal administration of streptomycin is a dangerous procedure, at least in the doses given in these 2 cases (50 and 100 mg., respectively) and should be used only when other methods of administration of the drug into the central nervous system are impossible. In such cases the drug should be instilled with extreme caution and terminated if there is any change in vital signs or neurologic status.

ALPERS, Philadelphia.

PROGESTERONE IN THE TREATMENT OF MIGRAINE. INDER SINGH, INDERJIT SINGH and DEVINDER SINGH, Lancet **1:**745 (May 31) 1947.

Singh and associates report the successful treatment with progesterone of 23 migrainous women who showed evidence of estrogen hyperactivity. The commonest manifestations of estrogen hyperactivity included disturbances of menstruation, such as excessive or prolonged periods. In all cases migraine could be induced by administering estradiol and was relieved by progesterone. Injections of distilled water had no effect on the migraine. The time of attacks corresponded to the time of excretion of free estrogen in the urine, namely, in the midmenstrual and the premenstrual period. The disappearance of attacks with the progress of pregnancy corresponded with the increased excretion of progesterone in the urine. The authors postulate that the estrogens might cause the headaches either by temporarily enlarging the pituitary gland, or their effect on the cerebral blood vessels, or by causing the retention of sodium and chloride in the body, predisposing to cerebral edema. All the patients had responded poorly to the usual methods of treatment. The name of "estrogenic migraine" is suggested for this condition.

MADOW, Philadelphia.

ELECTRIC SHOCK THERAPY UNDER ANESTHESIA WITH AND WITHOUT CURARE. P. KIELHOLZ and J. HEUSCHER, Schweiz. med. Wchnschr. **79**:592 (July 2) 1949.

Kielholz and Heuscher have given 120 electric shock treatments with the patient under thiopental (pentothal®) anesthesia, occasionally combined with curare. When only thiopental is used, 1 cc. of a 5 per cent solution is injected intravenously each minute until the patient fails to react to a call. Only then is the electric shock apparatus brought into the room, and the shock treatment given in the usual manner. After the shock the patient is kept under observation but is allowed to waken spontaneously. If curare is administered in addition, the thiopental solution is given first until the necessary depth of anesthesia has been obtained. Then the computed quantity of curare is injected through the same needle within two minutes. After the lapse of an additional three to four minutes (maximal hypotensive effect of curare), electric shock is induced. Immediately after the shock, 1 cc. of prostigmine methylsulfate is injected into the vein, and the patient is watched until he wakens. The authors say that the method which they use resembles that described by Brody. They stress that the combination with anesthesia makes it possible to employ electric shock therapy even in patients who show extreme anxiety and in those who would reject it because of fear. Shock treatment with the patient under anesthesia can be given even to those over 50 years of age.

J. A. M. A.

Experimental Pathology

SPINAL OSTEOPOROSIS, CAUSE UNKNOWN. H. J. BURROWS and G. GRAHAM, Ann. Rheumat. Dis. **6**:129 (Sept.) 1947.

Burrows and Graham review observations on 53 patients with spinal osteoporosis of unknown cause collected from the literature and from their own experience. The condition occurs in middle-aged and elderly persons. The authors consider the osteoporosis as the result of deficient ossification, which, in turn, is perhaps related to a long-continued deficiency of such dietary constituents as calcium, phosphorus and ascorbic acid; it is not due to vitamin D deficiency, as was believed at first. The cause is still obscure. Although generalized osteoporosis can sometimes be demonstrated, a material degree of porosis is confined to those bones which in the adult contain red marrow, namely, those of the spine, limb girdles and thoracic cage. Only the lumbar and thoracic vertebrae undergo sufficient porosis to suffer material deformity. The chief chronic symptom is backache, oftener lumbar than thoracic. The pain is usually worse with activity and is relieved by rest. Other complaints are stiffness, deformity (including diminution of stature) and a sensation of weakness of the back. Acute symptoms occur in about half the patients. A sudden, agonizing pain may be felt in the back when performing some trivial movement. Sometimes something is heard or felt to snap in the back. The patient may scarcely be able to move and usually spends several days in bed, getting relief from rest and warmth. The symptoms are thought to be due to a pathologic fracture of a vertebra. The symptoms and roentgenologic changes are explicable in terms of the plasticity and fragility of the vertebrae. Nearly every patient in this series was provided with a plaster bed. Most of them were fitted also with a spinal support. The diet was adjusted, and varying amounts of calcium, phosphorus and vitamin D were given. The clinical improvement which usually resulted from the treatment was not accompanied with increase in calcification.

J. A. M. A.

Society Transactions

NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY, AND THE NEW YORK NEUROLOGICAL SOCIETY

S. Bernard Wortis, M. D., *Chairman, Section of Neurology and Psychiatry in the Chair*
Combined Meeting, Dec. 13, 1949

Treatment of Painful Phantom Limb by Removal of the Postcentral Cerebral Cortex. Dr. C. G. de Gutierrez-Mahoney.

The phenomenon of painful phantom limb has been a difficult one to treat. Various neurosurgical procedures, such as neurectomy, rhizotomy and anterolateral chordotomy, have been used, without very great success. In 1941 a man suffering from severe painful phantoms of two fingers which had been amputated a year previously was observed to have convulsions involving the side of the amputated fingers and to be relieved of his pain for some time after the convulsions. It was then felt that by an attack on his problem at the cortical level more relief might be obtained than by other methods. The postcentral cortex corresponding to the amputated fingers was identified by electrical stimulation with the use of local anesthesia and was extirpated. The result was good, and the report was published in 1944 (*J. Neurosurg.* **1**:156-162, 1944). With the cooperation of the members of the Harvey Cushing Society, who have made their material available, and with a review of the literature, a series of 28 cases has been assembled and analyzed in which resection of sensory cortex was done for relief of painful phantom; the results were good in 19, fair in 4 and poor in 5.

This paper is to be published in the *Journal of Neurosurgery.*

DISCUSSION

Dr. Francis A. Echlin: Dr. Mahoney has shown that phantom limb pain can be abolished, at least temporarily, by a surgical attack at the cortical level (excision of the postcentral gyrus).

I should like to develop briefly the thesis that phantom limb pain can rarely be relieved by a surgical attack directed against the mere interruption of anatomic pathways for pain impulses between the periphery and the cortex. Whatever surgery may accomplish would appear to be the result of the interruption, breaking up or alteration of some abnormal physiologic mechanism that has taken place in the central nervous system.

It has been the experience of many that surgical interruption of pain pathways at the peripheral level only occasionally relieves phantom limb pain. The same has been true of surgical section at the spinal cord level, whether it be chordotomy or section of the posterior columns.

Adequate section of pain pathways at higher levels to relieve pain, that is, to shut off all pain impulses from the cortex, is probably impossible. This evidence has been adequately presented by Walker, Dandy, Evans, Gardiner and others. These authors have shown that pain may be appreciated on the opposite side of the body after hemidecortication, destruction of one thalamus, including the nucleus of termination for the spinothalamic tract, and section of the mesencephalic tract.

Walker has also shown that pain is appreciated from the periphery even after bilateral decortication with degeneration of both thalami. There is, of course, a wide thalamocortical projection to the cerebral cortex apart from that to the postcentral gyrus.

I should like to discuss some of the abnormal physiologic mechanisms that may be responsible for phantom limb pain. Livingston's theory of the vicious circle is probably the most intriguing explanation (Livingston, W. F.: Pain Mechanisms, New York, The Macmillan Company, 1944). In brief, he postulates that a source of irritation at the periphery may set up impulses which bombard the spinal cord, where they create a state of abnormal activity in the internuncial neuron centers. If the source of irritation is allowed to continue, the abnormal activity in the spinal cord may take on a momentum of its own, and a form of reverberating circuit may be set up. For instance, impulses at the spinal cord level may bombard the thalamus, which, in turn, discharges into the cortex. Impulses from the cortex reactivate the thalamus until a vicious circle of activity is established. As he points out, the vicious circle may sometimes be broken by its interruption at the periphery or at higher levels. It is generally known that sometimes a single procaine block of the sympathetic chain (as in a case reported by Livingston) may abolish the pain for years. Similarly, it is possible that removal of the postcentral gyrus may also break the vicious circle. Usually, however, the process sets itself in motion once more.

I recently heard Gerard postulate the development of hypersynchronous discharges from the thalamus. In brief, this theory is based on the fact that groups of nerve cells may take on synchronous activity when shut off from certain other incoming stimuli. For instance, this is what happens in the alpha rhythm when the eyes are closed. Theoretically, in the thalamus hypersynchronous activity may take place when a limb is amputated. When this occurs, the afferent discharges in many large fibers subserving postural or discriminative sensibility are blocked.

The thesis that the postcentral gyrus itself may become hypersensitive seems valid and could be fitted into Livingston's general theory.

DR. PHILIP R. LEHRMAN: I should like to ask a psychiatric question in regard to this neurosurgical condition. Some years ago, while working in the Vanderbilt Clinic, Hubert Howe made studies on postoperative neuroses, and I helped him. Though we did not complete the studies, we obtained some impressions as to the pathoneurotic mechanism involved. Briefly, if the organ operated on has a specific symbolic significance in the mental life of the patient, a subsequent condition develops which might be called a pathoneurosis. I should like to ask whether any such studies have been made on the patients reported by Dr. Mahoney.

DR. HAROLD G. WOLFF: May I ask Dr. Mahoney to describe exactly what was experienced by his patients after operative removal of parts of the cortex? Did they have phantom limb, even though not painful? Did they perceive pain in the usual way from pinprick in areas adjacent to the removed part? Did they perceive deep pain in the usual way, as on muscle squeeze? If they had pain or phantom limb pain, were they indifferent to it?

DR. ALEXANDRA ADLER: Did the relief reported in these cases mean relief from pain only? Was that parallel with any change in the phantom limb? Did the phantom limb disappear in those cases in which the pain was relieved? If it persisted, was there any change of position of the phantom limb after operation? Such observations might contribute greatly to knowledge of the importance of central and/or peripheral factors, respectively, in relation to the phantom limb.

For instance, it is known (Adler, A., and Hoff, H.: *Monatsschr. f. Psychiat. u. Neurol.* **76**:80-84, 1930) that injections of procaine into the stump or freezing it with ethyl chloride may change the position of the phantom limb.

DR. E. JEFFERSON BROWDER, Brooklyn: Our results from dorsal chordotomy for phantom limb were published about a year ago (Browder, J., and Gallagher, J. P.: *Ann. Surg.* **128**:456 [Sept.] 1948), and we have had no further surgical experiences with the problem. I have had no experience at all with excision of the parietal cortex. A case was included in our small series in which excision of a part of the parietal cortex had been carried out elsewhere. According to the history, temporary relief was obtained, but shortly thereafter the situation was infinitely worse, as a result of recurring convulsive seizures.

I did not hear the entire presentation by Dr. Mahoney; however, the results of bilateral frontal leukotomy seem a pretty stiff price to pay for the relief of a painful phantom. It is true that one may largely abolish the complaints by such a procedure, but the final result is not very satisfactory. In properly selected cases there is a good chance of relieving the pain of a phantom part by dorsal chordotomy.

DR. C. G. DE GUTIERREZ-MAHONEY: With regard to the question of pathoneurosis mentioned by Dr. Lehrman, the psychologic aspect of this problem has been studied extensively, not only in this series but by other investigators, and it has to be borne in mind.

The types of pain encountered were principally burning, crushing, tearing, cramplike pains.

In reply to Dr. Adler's question, the phantom disappeared as well as the pain.

There were 2 cases with convulsions in this series. In regard to the criticism that leukotomy is too radical a procedure for treatment of this disturbance, it must be borne in mind that the condition of these patients is heartbreaking; most of them are desperate and ready to commit suicide. The percentage of narcotic addicts is high. The problem is one which demands radical measures, and in such circumstances leukotomy is not unreasonable.

DR. HAROLD G. WOLFF: Was there two point discrimination on the side adjacent to the part removed?

DR. C. G. GUTIERREZ-MAHONEY: The cortical resections were limited to the parts concerned, the phantom (amputated) limbs, which could not be tested for two point discrimination. Sensory perception in the other parts was normal.

Fibrous Dysplasia of the Skull. DR. EMANUEL H. FEIRING and DR. LEO M. DAVIDOFF.

Involvement of the skull is frequently observed in cases of fibrous dysplasia. It may constitute the sole manifestation of the disease, or it may occur in association with lesions elsewhere in the skeletal system. The vault or base or both may be implicated. The roentgenographic appearance varies from cystlike areas of diminished density to extensive hyperostoses. Cutaneous pigmentation and sexual precocity may be accompanying features (Albright's syndrome). The disease is primarily one of early life. When limited to the skull, it may be confused with the changes in bone resulting from a meningioma.

Three histologically verified cases were presented. One was that of a 9 year old boy in which roentgenograms of the skull revealed thickening of the bones of the orbit on one side, reminiscent of a meningioma of the sphenoid ridge. Another case was that of a man aged 28 with a mass in the frontotemporal region since early childhood. Roentgenograms disclosed extensive deposits in bone involving

both the calvaria and the base on one side, the maximum thickening of the vault measuring 3.5 cm. A meningioma of the tuberculum sellae was suspected in the third case, that of a woman aged 25 with unilateral optic nerve atrophy and a bony mass in the middle of the posterior portion of the anterior fossa.

DISCUSSION

DR. SAMUEL BROCK: We owe the authors a vote of thanks for calling attention to this lesion, which may not be as rare as has heretofore been believed. It is a fragment of a larger clinical picture which is of exceeding interest; I would refer you to Albright and Riefenstein's remarkably fine monograph on the subject (The Parathyroid Glands and Metabolic Bone Disease, Baltimore, Williams & Wilkins Co., 1948). This syndrome in its full form seems to be due to a curious neural-hormonal upset in the organism. As Dr. Feiring said, it occurs in the full form in young girls, and it is polyostotic; that is, it involves many bones, especially the bones of the fingers, in which there are cystic changes. The girls affected have a remarkably precocious sexual development. Curiously, no sexual precocity has been reported in males. One of the cases reported was that of a woman who was observed at the age of 54. She had begun to menstruate at the age of 1 year, and was still menstruating at the age of 54. That woman had borne children. In the full form of the disease there is not only the remarkable change in the bone structure, but also an unusual brownish pigmentation of the body with irregular borders; this pigmentation is practically always unilateral, and it tends always to occur on the side on which the bony changes predominate. In the full-blown cases the bony changes are usually unilateral.

The important lesson that the authors point out is this: The lesion may involve one bone; that is, it may be monostotic, and it may occur in the skull, producing the syndromes they describe without the association of endocrine dysfunction and pigmentation. It should be kept in mind that the disease is a non-neoplastic process which is benign and often nonprogressive in its course. If it is not progressive, the lesion is not surgical; i. e., it should not be removed *in toto*. A biopsy specimen should be taken if the condition is suspected, but the lesion should not be removed unless it impinges on important nerve structures. In such a case partial removal may be indicated. Since the condition has been described, I have looked back, and I feel that I have probably missed a few cases and have regarded the lesion as an osteoma or a meningioma.

DR. BRONSON S. RAY: The last picture Dr. Feiring showed, which had somewhat the appearance of a meningioma of the tuberculum sellae, so much reminded me of a recent surgical case that I shall ask him a question about his case. My case is so recent, in fact, that I do not yet have the pathologic reports, but the patient had exactly the same type of calcified area in the midline encroaching on the tuberculum and the sphenoid bone as that in Dr. Feiring's case, and she had bitemporal visual field defects, a condition which induced me to operate. Operation revealed that the tumor was entirely extradural. It had none of the appearance of a meningioma, and since it lay largely in the region of the paranasal sinuses there was little indication for radical extirpation. The patient has survived operation well. If she has this disease, I should like to know whether we can rely on its not being a progressive process and whether we may hope therefore that there will be no progressive loss of vision.

DR. FRANCIS A. ECHLIN: I would like to ask about some cases I reported (Echlin, F. A.: Cranial Osteomas and Hyperostoses Produced by Meningeal Fibroblastoma: A Clinical-Pathologic Study, *Arch. Surg.* **28**:357-405 [Feb.]

1934) from the surgical pathology laboratory at Johns Hopkins Hospital. I reviewed all of Dandy's and Cushing's material and found 9 cases of probable fibrous dysplasia of the skull; I reported them as osteomas, with the intention of differentiating them from the hyperostoses produced by meningiomas. Some of these tumors reached the size of a grapefruit. The lesion was a huge bony prominence on the skull, which I called spongy osteoma. Geschickter went over all the material with me. Histologically, the tumors were almost identical with the type of lesion (fibrous dysplasia) described by Drs. Feiring and Davidoff. Some of them had a thin shell of bone over the surface, and at operation the perforator could be plunged through the shell into soft tissue—preosseus fibrous tissue, containing multiple little spicules of bone. There was very slight progressive enlargement in some cases. Most of the so-called osteomas occurred in childhood, but the patients were adults at the time of operation. The inner table of the skull was comparatively spared, and the extension was mostly outward, although it was occasionally inward. In some of these cases there was enlargement of the sinuses. Those lesions were all described as osteomas and have been redescribed as such in Geschickter's new book. I should be interested to know whether the authors believe these lesions are instances of fibrous dysplasia. Most of them arose from the vault, which is preformed in membranous bone. The base and the sphenoid bone are preformed in cartilage, and most of the cases reported by Dr. Feiring and Dr. Davidoff are from these regions, a fact which may account for the large number of giant cells seen in some of them. Some giant cells are seen in the spongy osteomas. It is interesting (but irrelevant) that true giant cell tumors presumably arise only in bones preformed in cartilage (especially perhaps the greater wing of the sphenoid).

DR. E. JEFFERSON BROWDER, Brooklyn: I should like to mention a few features of a case in which I operated in 1932. The patient presented signs somewhat comparable to those in the third case described by Dr. Feiring. No plaque meningioma was disclosed at operation. Subsequent to the surgical exploration there has been an extensive invasion of the skull, including the zygoma and the maxilla. The eye on the affected side is blind; however, there is no evidence of encroachment on the contents of the intracranial cavity. While it is possible that a plaque meningioma may have been missed at operation, it is extremely unlikely. In retrospect, it is highly probable that the lesion is similar to that described by Dr. Feiring. The case is somewhat contradictory to Dr. Brock's comment regarding the nonprogressive nature of such lesions.

DR. LEO DAVIDOFF: Essentially what this work has done for Dr. Feiring and me is to add another term to our vocabulary, a term which will have to be included in the vocabulary of every neurosurgeon, for this condition has undoubtedly been confused not only in our minds but in the literature with a great many similar conditions. The concept of the origin of these lesions from cartilaginous, as distinct from membranous, bone is not clear; nor is the origin of benign giant cell tumors from bone preformed in cartilage entirely established, for I have seen several such growths in preformed membranous bone.

I agree with Dr. Brock that some progression of this lesion must take place. I do not think that such a condition occurs full blown in the intrauterine stage. It may be true that after the lesion is disclosed by roentgenogram and followed over a period of years little progression is seen, but it must grow up to the point where it is first observed. The patient of ours who was operated on and died forty-eight hours later had a mass which appeared like an eggshell, with the thickness of the shell no greater than that of an ordinary egg; the shell once rup-

tured, soft debris of bony spicules and soft tissue was encountered, with the histologic character here shown. The patient did well for forty-eight hours and then suddenly died. We do not know the cause of her death; she may have had some other disease, of an endocrine nature, that we were not able to detect, even post mortem.

Dr. Browder's question is extremely interesting, for I can remember a number of cases of meningioma of the sphenoid wing in which I was unable to demonstrate any intradural tumor and was a great deal puzzled about it. It may be that this condition explains such an operative disclosure. Most persons with meningioma of the sphenoid wing are middle-aged women, and the cases I have referred to were also those of persons of that age and sex; yet they may have been instances of this disease. In the case of fibrous dysplasia of bone, it is rather encouraging that if one cannot remove the lesion completely the patient may still get along well. Thus, if the lesion compresses vital structures and decompression is made, one may anticipate only a very slow progression of the disease.

Dr. Emanuel H. Feiring: Dr. Ray raised the question whether he might anticipate further progression of visual loss in his case of the bitemporal visual field defect. As has been pointed out by Dr. Davidoff, the lesion either progresses very slowly or tends to become stationary after the patient reaches adult life, but occasionally it may progress more rapidly. H. L. Jaffe (*Bull. New York Acad. Med.* **22**:588, 1946) reported a case in which the tumor involved the vertebral column and Dr. Ira Cohen performed a laminectomy; I think he had to do a second one, owing to regrowth of the tumor. Dr. Echlin's description of minimal thinning of the inner table and maximum expansion outward is fairly characteristic of the process in some cases.

Psychiatric Aspects of Rehabilitation. Dr. Morris Grayson (by invitation).

This paper represents a preliminary study of the contributions that psychiatry can make to the relatively new field of rehabilitation. Rehabilitation requires an understanding of the total patient, whether his condition has been diagnosed as paraplegia, multiple sclerosis, paralysis agitans or some other disabling physical disease. The emotional problems of these disease entities, as well as the physical problems, have to be dealt with.

In order to understand these problems, there must be a complete study of the sensorial, intellectual and personality assets of the patient. The focus must be on the abilities, and not on the disabilities.

Workers in the field of rehabilitation must be ever aware of their own attitudes toward disability. Two cases of paralysis agitans were briefly discussed to show the complicating aspects of countertransference in rehabilitation and the help that a psychiatrist can give to the medical staff, the family and the patient in working out the reciprocal emotional problems. These problems represent, on a smaller scale, the attitudes of society toward the disabled. Psychiatry can orient the staff toward objectivity in dealing with emotional problems.

The concept of "acceptance" of a disability constitutes the core of functional rehabilitation. However, "acceptance" can take place only if the disability can be integrated into the body image and its defenses. Psychologic rehabilitation consists essentially of a fortification of the defenses that the patient himself is struggling with. The psychiatrist is aided in this process by psychologic testing and careful evaluation of the social situation by the social worker.

DISCUSSION

DR. HOWARD A. RUSK: In this country our age expectancy has increased from 46, in 1900, to the present figure of 68.5 for males and 70.5 for females. A recent survey made by the Department of Public Health at Yale University showed that 12 per cent of the population of New Haven are suffering from chronic disease or disability—a third of these being so badly damaged that they are unable to work and a third being under the age of 25. The following figures from the report of the Administrator of Veterans for the fiscal year 1947 give a good idea of what we have to expect: There will be almost as many World War II veterans (3,404,000) alive at the turn of the next century, 2000, as there were World War I veterans (3,727,000) on June 30, 1947. The average age of the World War II veterans in 2000, however, will be nearly 78, as compared with the present average of 55 for World War I veterans and 72 for Spanish-American War veterans. As of June 1948, World War II veterans had attained an average age of 29.8 years.

We in this country shall have to do something about retirement on chronologic age rather than physiologic age, and it seems fitting to note at this point that Harvey Cushing was retired from Harvard at the age of 65 and went to Yale thereafter, where some of his most dynamic work was done. If we do not do something about this attitude toward age, and about utilizing the residual abilities of our chronically ill and training our physically disabled to take their place in our economic system, by 1980 there will be for every able-bodied worker in America 1 person who is over 65 or chroncally ill or disabled.

The rehabilitation service in a hospital is organized as a service department, just as is the roentgenology department or the laboratory. It is designed to teach people to live, and if possible to work, with what they have left. As Dr. Grayson has said, this is not a one man job. It can be done only as teamwork. My colleagues and I have the feeling that a full rehabilitation program should start when definitive care becomes secondary and training primary. These crippled patients do better when they are in a group, and they are actually helpful to each other. We find that the quadraplegic patients feel sorry for the paraplegic patients and the paraplegic patients feel sorry for, and want to help, the patients with multiple sclerosis, the patient with his hand off is glad he can run; the man with his legs off is glad that he can use his hands. We have found that the use of group interests, the "help the other fellow" attitude and fundamental humanity, has been an unfailing therapeutic aid in our program.

Our experience has demonstrated the necessity for a "complete" program, which obviously calls for control of the patient in the training program. We feel, as Dr. Grayson has said, that the psychiatrist, in dealing with a disability, is dealing not with a set pattern, but with a body and a psyche with "a pack on its back." We feel we can best serve in this new-old field of medicine by helping to teach these patients to live a life of usefulness with what they have left.

DR. MORRIS HERMAN: It should be noted that Dr. Grayson, in the field of psychiatry, is doing a pioneer service in regard to rehabilitation. In rehabilitation, as well as in other fields that psychiatry is penetrating, there are two general tasks that psychiatry can perform. One is to determine the common elements that are present in a particular field as it pertains to the material to be dealt with. Despite Dr. Grayson's statement that there is not a multiple sclerosis type or a cancer type or a paralysis agitans type, the clinician thinks of the common features in these diseases. I expect, therefore, that there are common features in the psychiatric aspects of these illnesses, even though there may not be specifically a multiple sclerosis type or a paralysis agitans type, in the sense that there is a fixed per-

sonality constellation which leads inevitably to the development of the particular disease. I believe every illness has some common factor which produces an effect on the personality of the patient when it is developing; certainly, defects of themselves have some common elements that result in a specific psychiatric evaluation and determination in the individual patient.

DR. ALBERT BRYT (by invitation): I should like to emphasize what Dr. Grayson said, namely, that the whole personality has to be considered in each case. There does not seem to be any evidence from our research on the facially disfigured that would indicate what sort of rehabilitation might be possible as a result of the correction of the patient's facial defect. The family constellation which influenced the patient's development is of importance, and whether the defect was congenital or acquired through accident or disease must be considered.

Just as cooperation between the psychiatrist and the other members of the team is indicated for the best results in rehabilitation of the paralyzed, so in cases of facial disfigurement perfect teamwork between surgeon and psychiatrist is of the essence.

In some cases difficulties in interpersonal relationships occur which are not eliminated as a result of correction of the facial defect, but which may even be aggravated. Before any corrective operation is undertaken in such instances, the patient needs to be prepared for it psychologically. This preoperative training, in turn, can be done only on the basis of a thorough understanding of the personality makeup.

It is important to stress the difference between the congenitally deformed and those with facial disfigurement due to accident or disease. I believe the points Dr. Grayson made will apply to the latter group. The defense mechanisms, the need the patient may have to be dependent, the egocentric satisfactions he may derive from his disfigurement, what has been described as ego strength, are factors that must be considered with particular care.

The repair of a facial disfigurement, although satisfactory surgically and cosmetically, may not be to the patient's liking, owing to his unconscious needs. Repeated returns for more surgical treatment will make the patient an invalid, as a result of a procedure which was aimed to rehabilitate him. The cooperation between surgeon and psychiatrist will tend to eliminate those occurrences.

DR. MORRIS GRAYSON: When our team started the project, the first question asked of us was, "Can you tell us something about the sexual functions of the paraplegic?" Dr. Herman has raised this question, and I think it is an extremely important problem. The sexual function of the paraplegic patient is a subject in itself. It is the problem that still requires a great deal of research. The best information we have been able to obtain has been collected by the question and answer method. I submit that this is a totally inadequate way. It is just as difficult to gather information about the sex life of the paraplegic patient as about that of the nonparaplegic person. There is, first, the problem of the method of gathering information and, second, that of interpretation. It is my impression that only through psychoanalysis will one be able to learn the true meaning of the movement of the libido from the genital area to other parts of the body, if such is the case. What we do know so far is that sexual function in the paraplegic person is variable. We cannot predict genital function with any certainty on the basis of neurologic involvement. We know that tactile sensations of the genital organs are decreased in both sexes; however, we do know that erotic sensations may be experienced. One patient described these sensations as like the memory of the erotic sensation. It was as though they were an "as if" phenomenon. Other

patients described the sensation as a memory of urethral pressure. Other patients described orgasms in which the climax was reached by intense sweating and tingling of the whole body—particularly of the forehead—this without ejaculation. Another aspect of the investigation of the libido in paraplegic patients is the study of dreams and fantasies. Our work to date suggests that frank sexual dreams and fantasies do take place in the early part of the illness but later give way to walking dreams, which, of course, require further study for an understanding of their sexual significance. Overt complaints of sexual impotence come from males, and rarely from females. In males, sexual impotence appears to play a dynamic role when rehabilitation is attempted. It appears to play a much less important role in females.

Book Reviews

A Text-Book of Psychiatry for Students and Practitioners. By Sir David Henderson and the late R. D. Gillespie. Seventh edition. Price not given. Pp. 740. Oxford University Press, Amen House, Warwick Sq., London, E.C. 4, 1950.

This is the most readable of all textbooks of psychiatry. The senior author has carried on the tradition after the death of his eager collaborator and has turned out a reasonably good revision, including many of the advances of the past decade. Yet most of the descriptions have been repeated from previous editions, extending back almost a half-century, and the case reports are those of World War I. The approach is Meyerian, so far as concepts and classification is concerned, although considerable space is given to other formulations. Psychoanalysis, narcoanalysis and physical methods of treatment are discussed in some detail, and with skeptical appreciation of values. Many passages will delight the reader by their clarity of expression and their cogency. Personal views are distinctly, though not dogmatically, expressed. This work is not a catch-all of psychiatric theory and treatment, but is pragmatic in its expression, based on many years of teaching, study and experience.

Much of the material dealing with psychopathology could be further compressed, or separated from current chapters as historical introductions. The section on heredity would benefit from inclusion of the twin index studies, which are now numerous and well documented. Abreactive technics are sparingly dealt with. It is surprising to find in this standard work more skepticism in regard to the therapeutic value of psychoanalysis than to that of psychosurgery. Legal aspects of psychiatry, including the celebrated McNaghten case, are covered in satisfactory fashion. There is also rather extended consideration of the varied rulings in the different parts of this country. There is some carelessness in regard to references, but the index is a very complete one. Unlike most medical treatises, the text is not enlivened with illustrations. The book is readable because the authors have concentrated on clear exposition, including definition of terms. They have avoided profound speculations in the misty realms of the unconscious, and when it was necessary to present contrasting theories they have held themselves to the minimum for purposes of clarity. They have produced a useful book for the student of psychiatry.

Introduction à la psychochirurgie. By P. Puech, P. Guilly and G.-C. Lairy-Bounes. Price, 520 francs. Pp. 167, with 13 illustrations. Masson & Cie, 120 Boulevard Saint-Germain, Paris, 6e, 1950.

Puech died before this small volume could be written, but his assistants have written it almost in the first person, since Puech impressed his ideas so strongly on them. The book contains a rather well integrated summary of the work of many years carried out by the senior author and reported by him from time to time. Puech extended the concept of psychosurgery to all procedures carried out on the nervous system for the relief of mental symptoms, whether or not there were gross lesions present. Thus, he (through his colleagues) teaches that psychosurgery may be "lesional," as well as "functional." Most authors follow Freeman and Watts in their concept of psychosurgery as consisting of operations on the anatomically normal brain for the purpose of relieving mental disorders. Puech, however,

begins with a consideration of tumors and the results of their extirpation and passes on to trauma and disturbances of cerebrospinal hydrodynamics. In this discussion, he restricts himself properly to the mental symptoms produced by these abnormalities. He makes a special case for the disturbances of pressure within the cranial cavity, citing numerous instances in which mental symptoms cleared up after procedures such as spinal puncture, air insufflation and injection of saline solution. In this connection, he pays much attention to the blocking of fluid flow around the chiasm, as visualized by pneumoencephalography. For him, the condition of intracranial hypotension is just as important as that of hypertension, although this subject appears to have been more or less of a hobby with him.

Functional psychosurgery is taken up in the same systematic fashion, with consideration of lobotomy, lobectomy, topectomy and thalamotomy. The monograph contains a survey of 223 lobotomies performed by him, mostly by the Freeman-Watts method. The operative mortality was 3 per cent, and epilepsy developed in three of 73 patients followed. Indications and contraindications follow the standard pattern; lobotomy is employed for the relief of emotional tension and is not worth while unless tension is severe. With tension as the outstanding symptom, the operation may be employed successfully in a variety of mental disorders, including painful conditions. The chief contraindications to lobotomy lie in the personalities of the patient and his family. Puech gives a novel reason for not operating on some patients: "In this difficult phase, when a new personality is developing . . . a premature return to the family might lead to disaster." He advises choice of patients on the basis of the psychiatrist's opinion, rather than on the solicitation of the family. As far as the choice of operation, Puech advises close attention to the minimal operation that will produce effective results. Massive lobotomy is being replaced by more selective operations. The pupils of Pierre Puech have erected, in this modest monograph, a very satisfactory monument to their chief.

Cerebral Circulation in Health and Disease. By Karl F. Schmidt. Price, $2. Pp. 78. Charles C Thomas, Publisher, 301-307 E. Lawrence Ave., Springfield, Ill., 1950.

This monograph reviews the investigation of cerebral circulation between 1887 and 1949.

The review begins with a summary of the comparative anatomy of cerebral arterial and venous systems of man and laboratory animals as a means of evaluating the application of results obtained in laboratory animals to man.

The chapter on anatomy is followed by a summary of the physiology of cerebral circulation, wherein the author stresses the fact that the blood vessels of the brain possess a capacity for intrinsic control and are subject to all the influences that affect the circulation elsewhere in the body. One finds that the influence of arterial blood pressure on cerebral circulation is not completely clarified, but the preponderance of information indicates intrinsic control, with the circulation of the brain tending to follow passively changes in systemic arterial pressure to a greater extent than that of most other organs. The vasoconstrictor and vasodilator impulses carried over the sympathetic nerves influence the extracranial vessels more than the intracranial vessels. Evidence is against continuous sympathetic control of the tonus of cerebral blood vessels, as well as against the likelihood of cerebral angiospasm from sympathetic impulses. Cerebral vasodilation can be mediated in experimental animals over the facial nerve. Metabolic products influence the intrinsic control; decreased carbon dioxide and high oxygen (85 to 100 per cent) levels cause significant cerebral vasoconstriction. Increased carbon dioxide (5 to 7 per cent) or decreased oxygen (10 per cent) tension yields cerebral vascular dilation. Acid agents cause dilation, and alkaline agents

constriction; however, the two effects are neither as marked nor as consistent as the effects of changes in carbon dioxide tension. The effects of heat, cold, potassium and calcium are inconclusive, but as yet they indicate nothing more than a weak influence on the cerebral vascular tone.

The available evidence on hormones indicates that epinephrine given systemically will increase cerebral blood flow, dilate cerebral vessels and exaggerate any existing tendency to hemorrhage. Posterior pituitary has no significant effect on the cerebral blood vessels. The effects of other hormones have not been studied. Carbon dioxide and glyceryl trinitrate are the best cerebral vasodilators, with carbon dioxide heading the list in that it decreases extracranial flow while increasing intracranial flow. The other drugs to which cerebral vasodilation is attributed produce greater extracranial vasodilation, thus probably bringing about a redistribution of blood at the expense of cerebral blood flow. The extreme is found with histamine, with which extracranial flow is increased and intracranial flow is decreased. Aminophylline decreases the cerebral blood flow in man. Decrease in carbon dioxide tension gives the strongest cerebral vasoconstriction. Intracranial vessels are relatively insensitive to agents that constrict vessels elsewhere. No drugs have constricted the cerebral blood vessels strongly, and only a few have any constrictor effect at all. Cerebral blood vessels undergo an intense constriction in hypertension, as do the blood vessels in other parts of the body. The cause of this is unknown. Hypertension has not yet been experimented with in investigation of cerebral circulation. Studies of cerebral circulation associated with functional activity have shown that the significant changes are all in the direction of vasodilation.

Dr. Schmidt devotes the last chapter of his monograph to the results of cerebral investigation in man obtained through the use of Kety's method, which applies to the measurement of cerebral blood flow the Fick principle. The following interesting facts are revealed: hyperventilation produces a decrease of 32 to 36 per cent in cerebral blood flow. Increased carbon dioxide tension yields the highest mean cerebral blood flow. Inhalation of high oxygen concentrations decreases cerebral blood flow about 13 per cent. A mixture of 10 per cent oxygen and 90 per cent nitrogen yields an increased cerebral blood flow. Thiopental decreases cerebral vascular resistance and decreases cerebral metabolism. The latter reduced state was exceeded only in severe insulin coma; yet narcosis of these subjects was light. This decreased oxygen consumption was associated with decreased functional activity, suggesting that many narcotics when judiciously used may prevent irreversible damage to the brain in instances of prolonged anoxemia, pulmonary edema, severe hypotension or high intracranial pressure. In normal subjects, aminophylline decreases cerebral blood flow and increases cerebral vascular resistance. Ten minutes after a convulsive seizure in epileptic patients or after metrazol or electric shock, one finds a decrease in cerebral blood flow and oxygen consumption, with increased arteriovenous oxygen differences and vascular resistance, as well as acidosis, the acidosis having been responsible for the vasoconstriction. Insulin increases the cerebral blood flow and decreases cerebral oxygen consumption and arteriovenous oxygen difference without change in vascular resistance. Cerebral glucose consumption fell 83 per cent, whereas oxygen uptake fell only 45 per cent, indicating to the author that the brain utilizes foodstuff other than glucose or consumes its own carbohydrate stores. Oxygen consumption was reduced an average of 19 per cent in patients with varying degrees of confusion and about 40 per cent in patients in coma. Patients with brain tumor, some conscious and some in coma, revealeded increased cerebral vascular resistance with reduced cerebral blood flow and oxygen consumption and increased

arteriovenous difference. Ventricular drainage did not improve any of the functions appreciably. In cases of cerebral hemangioma, there were three times the normal cerebral blood flow and a decrease in cerebral vascular resistance and arteriovenous oxygen difference. Cardiac output was increased about 30 per cent. Lobotomized patients revealed a decrease in cerebral blood flow of 23 per cent, an increase in cerebral vascular resistance of 23 per cent and a decrease in oxygen uptake of 16 per cent. Patients with hypertensive vascular disease with normal cerebral function showed normal cerebral blood flow, oxygen consumption and arteriovenous difference and an increased cerebral vascular resistance, thus affording practically perfect cerebral homeostasis. These patients were compared with patients with hypertensive vascular disease in whom the sympathetic impulses were blocked by various means. Only block of the stellate ganglion failed to decrease cerebral vascular resistance; as well, it also failed to increase cerebral blood flow. In patients with hypertensive vascular disease and mental deterioration, there was a decrease in cerebral blood flow and oxygen consumption. Polycythemia gave the highest values for cerebral vascular resistance and the lowest values for cerebral blood flow found. In mild cases of diabetic acidosis there was a decrease in cerebral oxygen consumption, arteriovenous oxygen difference and cerebral blood flow, whereas in the severe cases the cerebral blood flow was increased, in the face of decrease in mean blood pressure, and therefore in cerebral vascular resistance.

Cerebral Angiography. By P. Almeida Lima. Price not given. Pp. 221, with 181 illustrations. Oxford University Press, 114 5th Ave., New York 11, 1950.

This is the first book in English on this fascinating development in neurologic diagnosis. Considering the number of articles on the subject that have appeared in periodical literature, it seems as though the author had accomplished his work just in time to establish his claim to authority in the field first opened by his chief, Egas Moniz. This is no mere translation from the Portuguese, however, but is written in idiomatic English, acquired, at least in part, while the author was carrying forward his studies under Sir Hugh Cairns. Both Moniz and Cairns have contributed brief forewords, which are not needed to establish the worth of the volume.

Almeida Lima prefers injection of a colloidal suspension of thorium dioxide (thorotrast®) after exposure of the common carotid artery on each side, though he admits that other substances and other methods may be found useful. Serial films, taken at intervals of two seconds, are essential, while frontal views and stereoscopic exposures are considered more or less as luxuries. The author sticks to his theme and rarely diverges from the essential; hence there are few passages that the reader will wish to skip. The reproductions are excellent, and a number of diagrams explaining some of the more obscure roentgenograms will aid in the interpretation of the films.

Cerebral angiography is the only method of value in the diagnosis of vascular lesions of the brain, such as aneurysms, thromboses and arteriovenous abnormalities of one sort and another. By means of angiography, not only the size and location of the lesions but also the source of the circulation and the apparent operability may be determined. The author stresses the fact that much more is now known about these aspects than would have been possible before the advent of angiography. On the other hand, the angiographic alterations in acute head injuries are much less specific, and the author does not even discuss the problem of intracerebral hemorrhage. Subdural hematoma is difficult of interpretation on lateral films but quite characteristic in frontal films.

The diagnosis of intracranial tumors is particularly stressed by the author, with a large number of demonstrative angiograms. Two aspects of the roentgenograms are particularly helpful: first, the displacment of normal vessels and, second, the circulation of the tumor itself. Meningiomas have a slow circulation through fine vessels and hence are revealed in the latter part of the series of roentgenograms as opaque masses with large surrounding veins. Astrocytomas are accompanied with marked displacement of vessels and small areas of vascularization. Glioblastomas reveal much less displacement of vessels but have a peculiar circulation of their own, often with arteriovenous fistulas and lakes, in which the contrast medium may be appreciably delayed in its course. Cysts, abscesses and tubercles are avascular and reveal their presence usually only by displacement of vessels.

This work, in some respects, must be regarded as a primer, because, even though it is the fruit of 25 years of work, the subject of angiography has expanded so rapidy during the past few years that the volume has not kept pace with latest developments. However, it is so clearly presented and so beautifully illustrated that it may well take a place as a foundation book for the study of the subject.

A Psychiatrist Looks at Tuberculosis. By Eric Wittkower, M.D. Price, 12 s, 6 d. Pp. 152. National Association for the Prevention of Tuberculosis. Tavistock House, N., London, W.C. 1, 1949.

In this very readable monograph, Dr. Wittkower summarizes the findings of detailed psychiatric interviews with 785 patients in various stages of pulmonary tuberculosis. The first section of the book deals with the behavior of these patients, in terms of reactions to the initial symptoms of the disease, to the diagnosis of tuberculosis and to the course of the illness. The second section outlines the various factors which determine such behavior—factors arising from the illness, from the patient and from the environment. The third, and final, section is a discussion of the relevance of emotional factors in the etiology and course of pulmonary tuberculosis. All three sections are characterized by a praiseworthy objectivity and freedom from theoretic bias.

Wittkower's study effectively disposes of many widespread misconceptions about the personality of the tuberculous patient. Many of the contradictory characteristics ascribed to these patients in the literature become understandable in the light of dynamic reactions of different personality types to the specific problems involved in this illness. Of interest to psychiatrists and general practitioners alike are the cases illustrating the manner in which the patient's emotional reaction to the illness while it is still undiagnosed often simulates a neurasthenic or depressive disorder. The book as a whole sheds much light on the relevance of psychiatric factors in tuberculosis. It should be rewarding reading, not only for all who are involved in the treatment and managemtn of tuberculous patients but also for all physicians interested in the interrelation of emotional and somatic disorders.

Neurological Anatomy in Relation to Clinical Medicine. By A. Brodal. Price, $14.75. Cloth. Pp. 496, with illustrations. Oxford University Press, 114 5th Ave., New York 11, 1948.

It is already clear from the preface of the Norwegian edition that Dr. Brodal does not mean this volume to replace standard textbooks of neuroanatomy, and many of the illustrations commonly used in the teaching of neuroanatomy are not included in this book. For the student who already has a basic knowledge of anatomy and neurology, Dr. Brodal's book, which is well known in Europe,

makes for interesting, profitable reading. The symptomatology is discussed in relation to anatomic and functional units to an extent that can hardly be done in the ordinary textbook of neurology. The text is well organized under such headings as the pyramidal tract; the somatic afferent, autonomic and optic systems; the cerebellum, etc., with subheads anatomy, functional aspects and symptomatology. Consequently, a wide range of diseases is surveyed. From the ambitious title, one could have expected a similar description of the hypophysis and the pineal gland. Furthermore, the anatomic and functional basis for symptoms referable to the spinal cord and peripheral nerves are important enough to clinical medicine to deserve a larger coverage. The study of agnosia and aphasia, with which many famous Scandinavian names are connected, is overshadowed by other subjects in connection with the discussion of cerebral localization.

In general, the book is clear and easy to read, carries a wealth of information and gives a logical explanation of many neurological symptom patterns which often appear confusing when the anatomic basis is not sufficiently stressed.

The Clinical Examination of the Nervous System. By G. H. Monrad-Krohn, M.D. Ninth edition. Price, $5. Cloth. Pp. 131, with illustrations. Paul B. Hoeber, Inc. (Medical Book Department of Harper & Brothers), 49 E. 33d St., New York, 1949.

Nine editions of any medical book in twenty years should vouch for its usefulness and popularity. In the last edition of this work, Monrad-Krohn has again presented his subject in a clear and simple way. Within its space, one would like to have seen a more detailed survey of the examination of the peripheral nerves than is now given. Galvanic and faradic stimulation is described at length, and the clinically more important electromyography is represented by only three lines. In general, however, the examination of the nervous system is well covered, and this new edition will no doubt be of great help to students and practitioners.

Vocational Rehabilitation of Psychiatric Patients. By Thomas A. C. Rennie, Temple Burling and Luther E. Woodward. Price, 75 cents. Paper. Pp. 133. Commonwealth Fund, Division of Publications, 41 E. 57th St., New York 22, 1950.

The authors, Thomas A. C. Rennie, Temple Burling and Luther E. Woodward, have contributed a lucid and revealing study of 215 psychotic patients after hospitalization: In this careful study, they have analyzed the needs and services of a vocational rehabilitation program for patients. The report follows the patient through an integrated and embracing program of vocational and personal counseling, training, job finding and placement, and physical restoration.

The responsibilities and problems of hospital and of rehabilitation bureaus in giving adequate vocational services to patients are discussed. The methods of cooperation between the two agencies and the difficulties encountered are described, and evidences of the success of rehabilitation efforts are presented.

This well formulated program evidences thoughtful insight into the needs and goals of patients who are recognized as productive and useful citizens of the community.

The authors are able to show that, by positive and constructive utilization of vocational rehabilitation, both patient and community can profit from the recognition of their specific needs in an enlarged program.

Rehabilitation requirements and limitations have been indicated by the study. The authors stress the desire for research and more conclusive technics in a

vocational rehabilitation program which would include persons with psychoneuroses, epilepsy and the upper level of feeblemindedness.

This study poses many questions which I feel will have to be answered in the immediate future by the community and those in responsible administrative positions.

As citizens we must all share the responsibility of providing adequate help to those patients who will become assets to a well integrated community; failure on our part will result in a tremendous loss to society in the social, economic and educational framework.

The questions posed by the work are these:

1. What is the relation of the cost of such a program to the requirements of the patient and his communty?

2. Do the benefits to the patient warrant increased financial responsibility?

3. What is the relation of the vocational rehabilitation program to the patient, his family and immediate environment?

4. What is the attitude of the patient toward his own need?

5. Can such a program be realistically related to the vocational opportunities afforded by the community?

6. How can we best make use of the resources and creative skills that patients have?

An extensive study is needed to show the social, economic and educational losses resulting from the inability of the community to absorb all of its potentially productive members. This problem is also directly related to the rapid increase in delinquents, psychopaths and chronic drinkers who cannot be successfully reintegrated into community life. These and potential patients will make an adequate adjustment dependent on building constructive habits and work goals. They require an understanding of their capabilities and their relation to society. Self-respect, feelings of adequacy and security can grow only in a soil provided by a community which cultivates the desires and goals of the patients by an adequate recognition and understanding of their personal problems. Through understanding the patient's interests, experience, education aptitudes and capabilities, we can formulate work goals compatible with the needs and best interests of patient, family and community.

Psycho-Analysis: A Handbook for Medical Practitioners and Students of Comparative Psychology. By Edward Glover, M.D. Second edition. Cloth. Price, $4. Pp. 367. Staples Press, Ltd., Mandeville Place, London; 70 E. 45th St., New York 17, 1949.

This is an excellent systematic account of psychoanalysis and psychiatric theory for general medical practitioners, psychiatrists and other students of psychiatry and comparative psychology. Glover is one of those master clinicians and teachers and fine medical authors which Britain is wont to produce. Their productions, while based, to be sure, on the work of authorities who have preceded them, are the refinement of their own thinking; in this vein one recalls S. A. K. Wilson, in neurology, and Wilfred Trotter, in surgery. There is perhaps nothing in this volume that has not been tested by Glover's own vast experience—would that this were true of more composers of medical articles and textbooks!

The opening third of the present volume is devoted to the theory of psychoanalysis, with chapters on the embryology of mind, dynamic aspects of mind, economics of mind, phases of mental development, dreams and symptomatic acts and symptom formation. In the preface the author notes that such progress as has been made in this field has been in filling in gaps left by Freud during

his sweeping advances, particularly in the direction of the preconscious factors in mental disorder.

The middle third of the book is devoted to clinical psychoanalysis; in general, there are discussions of clinical aspects, then etiological aspects and, finally, diagnostic aspects of the various clinical entities.

The final third of the volume is devoted to practical applications of psychoanalysis, together with a glossary of terms and a list of references for additional reading, with cogent reasons appended for their recommendation. A thorough index, occupying 15 pages, closes the book.

Since Glover is a foremost exponent of freudian psychology and an authority on all matters concerning psychoanalysis, it is to be expected that he should follow closely along the lines laid down by Freud, which from the standpoint of authoritative statement is all to the good. While one does not expect an opinion in a handbook such as this, it would be interesting to know the author's concept of the outcome of the race between deep-going, exploratory psychiatry and mental illness. Admittedly, the only satisfying understanding of behavior is that based on freudian doctrine; yet it is difficult to envision how these truths, which now are becoming very nearly self evident, may be effectively brought to bear against the great problem that mental disorder has become. Be that as it may, for anyone wanting an introduction to psychoanalysis or, on the other hand, a systemic review, this volume is among the best, if not the best, in the English language.

Current Therapy 1950. Edited by H. F. Conn. Price, $10. Pp. 736. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5; 7 Grape St., Shaftesbury Ave., London, 1950.

This is the second annual edition of this volume, designed to bring to the practicing physician the latest methods of treatment as used by the more than 250 contributors who have written it. Forty new contributors have been recruited for the 1950 issue, and sixteen additional subjects have been treated, probably some index of the suggestions received from readers by the editor and his consultants.

Dr. H. Houston Merritt, professor of neurology, Columbia University College of Physicians and Surgeons, is the consultant for nervous and mental diseases, and he has designated some three dozen or more contributors to describe therapy for diseases of the nervous system, which constitutes section 12, about 79 pages. Most, if not all, of the contributors are actively engaged in practice, though with the rare exception they are teachers as well.

Undoubtedly there will be quibbling by occasional specialist readers about the prescribed treatment for this or that symptom, since causation is often unknown and therapy is sometimes a personal matter. Indeed, several contributors writing on the same disorder are in obvious disagreement as to methods of therapy, indicating, of course, that none is satisfactory. The editor, Dr. Howard F. Conn, or the consultant for any section will want to hear from readers; the nature of the book demands that this be the case. As a starter, it might be asked why there is no mention of the curativeness of psychotherapy properly administered in narcolepsy?

The book represents an interesting departure from the usual medical publication and, while without much permanent value (how few medical books are!), will be of immediate importance to many physicians who must have the technical aspect of medicine always at their finger tips. The men who do the hard work of medicine will find comfort in this volume, since it is the most up-to-date and authoritative compendium of therapy.

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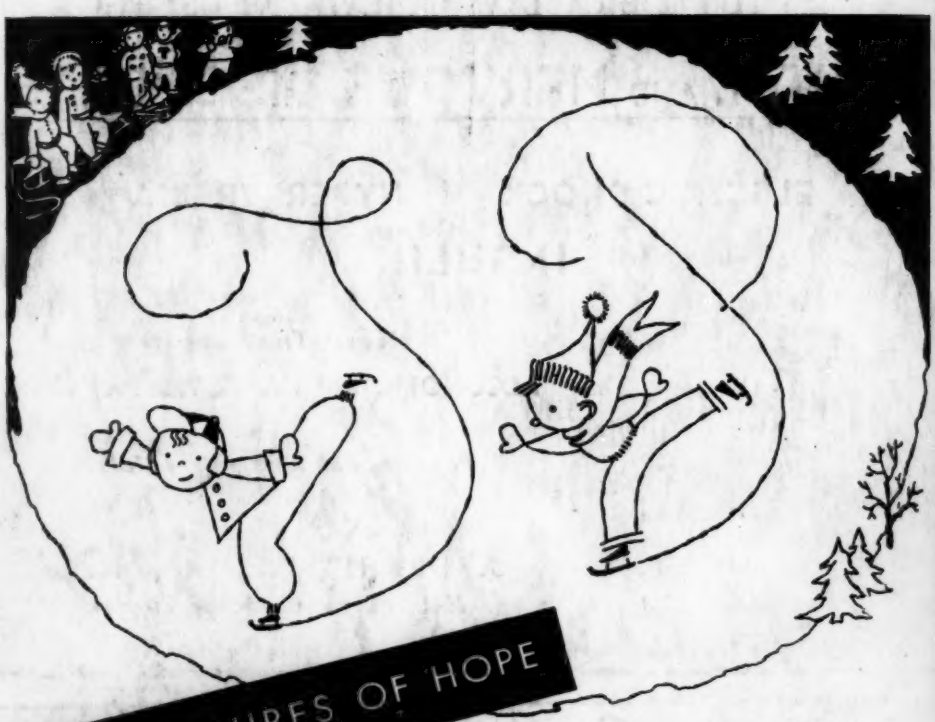

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